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Synthesis of 2-carboxyethyl- and 2-alkenylaziridine derivatives and their transformation into novel heterocyclic and carbocyclic compounds

Thesis submitted in fulfillment of the requirements for the degree of Doctor (PhD) in Applied Biological Sciences: Chemistry and Bioprocess Technology

Dutch translation of the title:

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The author, The promoters,

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Woord vooraf

‘Wat ook later moge komen, wat ook zij ons levenslot, steeds zullen wij blijven dromen van dat fijne Boerekot!’ Vaak hebben we deze woorden gezongen tijdens de vele VLK-activiteiten en na een mooie studententijd had ik het geluk mijn verblijf aan de faculteit bio-ingenieurswetenschappen te kunnen verlengen met 4 jaar, wat uiteindelijk geleid heeft tot dit doctoraatsproefschrift. Nu de tijd van gaan echt aangebroken is, besef ik maar al te zeer hoe mooi deze periode wel geweest is en zal ik inderdaad nog vaak terugdenken aan dat fijne boerekot. Graag zou ik van deze gelegenheid gebruik willen maken om een aantal mensen te bedanken die dit alles hebben mogelijk gemaakt.

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ronde van ‘komen eten’ dus verwacht jullie binnenkort maar aan een uitnodiging, deze traditie mag zeker niet verloren gaan! Wouter en Tamara wil ik bedanken voor het nalezen van mijn doctoraat. Ik bewonder je oog voor detail, Tamara, dat nog vele schoonheidsfoutjes uit de tekst en reactieschema’s haalde. Stéphanie, we hebben elkaar pas echt leren kennen tijdens ons thesisjaar maar ondertussen ben je een echte vriendin geworden. Bedankt voor alles wat je voor mij gedaan hebt en dat ik altijd op je kon rekenen, zeker de afgelopen maanden! Het zal wennen zijn je niet meer iedere dag te zien op de faculteit maar ik ben ervan overtuigd dat we elkaar nooit uit het oog zullen verliezen. Pieter, Els en Ans verdienen ook een woordje van dank, naast de hulp bij alle praktische zaken kon ik bij jullie altijd terecht voor een gezellige babbel. Also a special thanks to Prof. F. Formaggio for hosting me three months at the University of Padova, Italy.

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Stijn De Brabandere

Oktober 2014

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List of abbreviations

Ac: acetyl

(α-)ACC: 1-aminocyclopropanecarboxylic acid

Ac_3c: 1-aminocyclopropane-1-carboxylic acid

Ac_6c: 1-aminocyclohexane-1-carboxylic acid

Aib: 2-aminoisobutyric acid

Ala: alanine

$AMAc_3c$: 1-amino-2-(aminomethyl)-cyclopropane-1-carboxylic acid

Bn: benzyl

Boc: *tert*-butoxycarbonyl

Cbz: carboxybenzyl

DAB: L-2,4-diaminobutyric acid

DABCO: 1,4-diazabicyclo[2.2.2]octane

Dab-Pip: (*S*)-2,4-diaminobutanoylpiperidine

DAP: diaminopimelate

dba: dibenzylideneacetone

DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene

DDQ: 2,3-dichloro-5,6-dicyanobenzoquinone

DEAD: diethyl azodicarboxylate

DIBAL-H: Diisobutylaluminiumhydride

DIC: *N*,*N*'-diisopropylcarbodiimide

DMAP: 4-(dimethylamino)pyridine

DME: dimethoxyethane

DMF: dimethylformamide

DMSO: dimethyl sulfoxide

DPP: dipeptidyl peptidase

dr: diastereomeric ratio

EDC: 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide

ee: enantiomeric excess

equiv: equivalent(s)

Gly: glycine

hfacac: hexafluoroacetylacetonate

HOAt: 1-hydroxy-7-azabenzotriazole

LDA: lithium diisopropylamide

LiHMDS: lithium bis(trimethylsilyl)amide

m-CPBA: 3-chloroperoxybenzoic acid

MEM: β-methoxyethoxymethyl ether

Ms: methanesulfonyl

Mts: 2,4,6-trimethylbenzenesulfonyl

NBSH: 2-nitrobenzenesulfonylhydrazide

NMO: *N*-methylmorpholine *N*-oxide

NOESY: Nuclear Overhauser effect spectroscopy

Ns: nitrobenzenesulfonyl

Nu: nucleophile

oct: octanoate

PhF: phenylfluorenyl

Phth: phthalimido

ppm: parts per million

rt: room temperature

Ser: serine

Ses: $SO_2CH_2CH_2SiMe_3$

TBDMS: *tert*-butyldimethylsilyl

TEMPO: 2,2,6,6-tetramethyl-1-piperidinyloxyl

OTf: trifluoromethanesulfonate

TFA: trifluoroacetic acid

TFE: 2,2,2-trifluoroethanol

THF: tetrahydrofuran

TMS: trimethylsilyl/tetramethylsylane

Tr: trityl (triphenylmethyl)

Ts: *para*-toluenesulfonyl

1 Introduction and Goals

The discovery of non-proteinogenic (di)amino acids among natural products has significantly increased interest in this class of compounds as they may possess interesting biological activity and could also serve as valuable building blocks in the synthesis of new classes of bioactive compounds.[1] Furthermore, these non-proteinogenic (di)amino acids can be used for the design and synthesis of peptides, as substitutes of the original α-amino acids in order to modulate their structure and activity.[2] An important example is L-2,4-diaminobutyric acid **1** (DAB), which is a naturally occurring α,γ-diamino acid, present in certain *Lathyrus* species, and causes a type of neurolathyrism.[3] DAB has, among other effects, an antitumor effect, and is used in peptide design.[4] DAB residues are also found in polymyxins **2**, a family of cationic lipopeptide antibiotics produced by Gram-positive bacteria and active against many Gram-negative bacteria (Figure 1).[5]

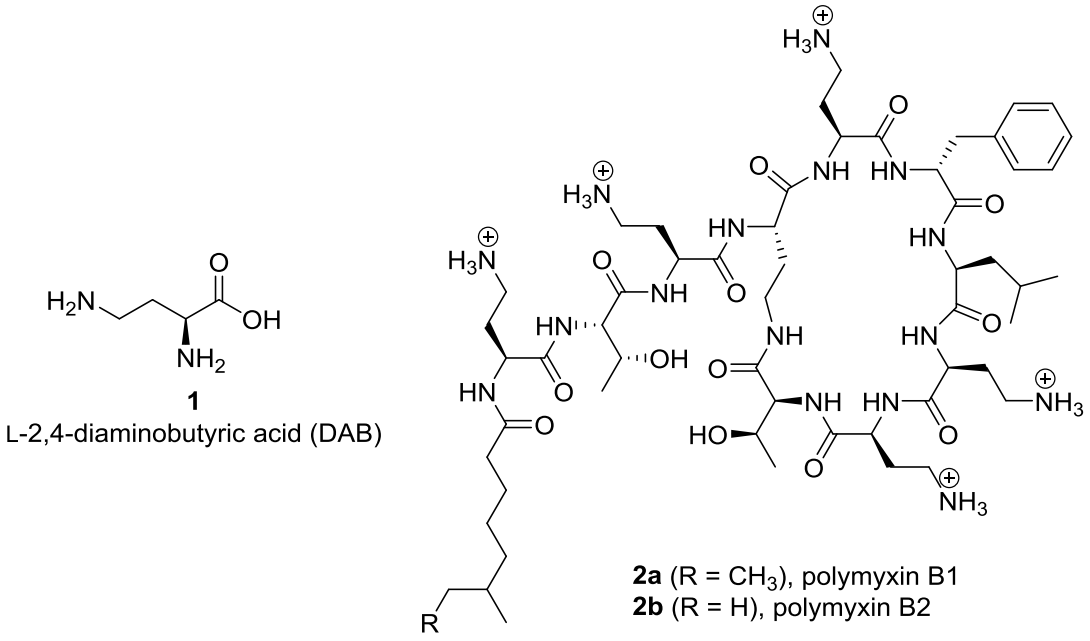
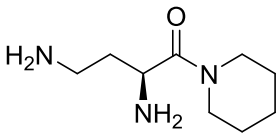


Figure 1

Recently, it was found that 2,4-diaminobutanoylpiperidines and analogues are excellent inhibitors of the enzyme dipeptidyl peptidase II (DPP II, also known as DPP7 and QPP).[6] Proline-specific dipeptidyl peptidases (DPPs) are enzymes that are capable to cleave off dipeptides at the *N*-terminus of peptides with preferentially proline at the penultimate position. Due to the unique structure of proline, relatively few enzymes are capable of doing so which makes this group an important protease family that may play an important role in the regulation of biological processes. Inhibitors of these DPPs have an interesting therapeutic potential, particularly in diabetes, oncology and

hematology. DPPIV is by far the most studied enzyme of this family and, therefore, other dipeptidyl peptidases with overlapping substrate specificities are often referred to as DASH-proteins ("DPPIV-activity and/or structure-homologues") and include DPPII, DPP8, DPP9 and Fibroplast Activation Protein α (FAP α). It is a successful target for drug design and several DPPIV inhibitors have already been accepted or are under review for the treatment of type 2 diabetes. Inhibition of DPPIV stops DPPIV-mediated degradation of incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), involved in the regulation of glucose homeostasis *via* stimulation of insulin secretion, inhibition of glucagon release and delay of gastric emptying, with an overall decrease of blood glucose levels.

(*S*)-2,4-Diaminobutanoylpiperidine (Dab-Pip) **3** was described as the first highly selective DPP II inhibitor and was used as lead compound for the synthesis of new derivatives (Figure 2).[6b,7] Very recently, the structure of the complex of human DPP II with Dab-Pip **3** was determined after co-crystallization.[6c] Although the exact function of the enzyme remains largely unknown, its widespread distribution in the human body suggests a general role for DPP II as one of the house-keeping proteins.[6a] The design of new highly selective inhibitors may be of great importance to unravel the exact mode of action of the enzyme and can give rise to new biomedical applications of these inhibitors.



3

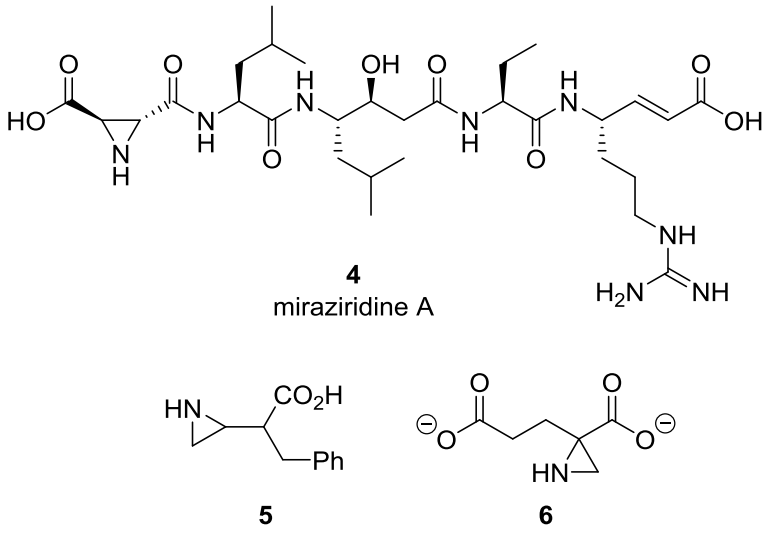
(*S*)-2,4-diaminobutanoylpiperidine (Dab-Pip)

Figure 2

Conformationally constrained carbocyclic and heterocyclic α-amino acid derivatives also received increased attention because of their unique biological activities and conformational properties that are useful in fundamental research on structure-activity relationships.[8] Linear peptides are highly flexible molecules that can adopt many conformations in solution of which only a few are responsible for their biological activity. The construction of novel peptide sequences, so-called foldamers and peptidomimetics, with incorporation of rigid amino acid surrogates to fold with predetermined secondary and tertiary structures provides very useful information on the bioactive conformation and results in beneficial physiological effects.

Aziridine-2-carboxylates[9] have shown their utility as inhibitors of diaminopimelate (DAP) epimerase[10], a key enzyme in lysine biosynthesis in higher plants and bacteria, and aspartic acid

protease,[11] whereas peptidic or peptidomimetic sequences containing an aziridine-2,3-dicarboxylate moiety are known cysteine protease inhibitors.[12] A representative example is miraziridine A **4** (Figure 3), found in the marine sponge *Theonella mirabilis*, being a nearly perfect "protease killer" which not only inactivates cysteine proteases but also reversibly inhibits aspartate proteases and serine proteases. Homologues of aziridine-2-carboxylates, such as β,γ- or γ,δ-aziridino acids, i.e. 2-(carboxymethyl)- and 2-(carboxyethyl)aziridines, have been far less studied as biologically active constrained heterocyclic amino acids.[13] Examples are 2-benzyl-3,4-aziridinobutanoic acid **5**, known as an inhibitor of carboxypeptidase A,[14] and aziridino-glutamate **6**, which is an inhibitor of glutamate racemase.[15]

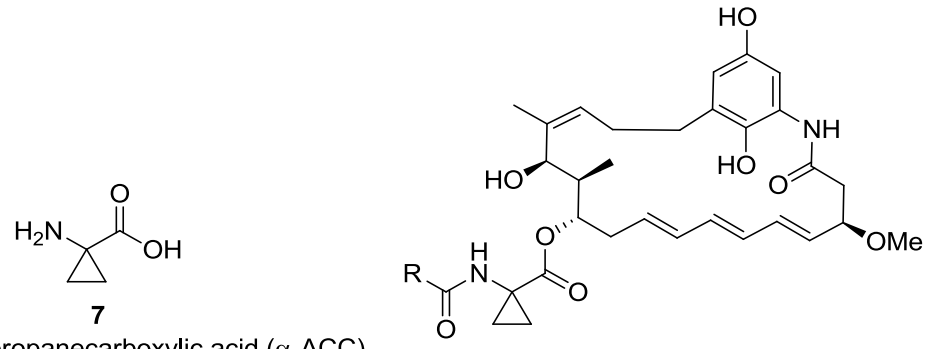


4
miraziridine A

5 **6**

Figure 3

None of the naturally occurring amino acids containing a cyclopropyl group is proteinogenic, but most of them are associated with some interesting and important biological activity, which is also the case for some of the cyclopropyl analogues of the proteinogenic amino acids. Cyclopropylamino acids are often classified as “methanoamino acids”. 1-Aminocyclopropanecarboxylic acid **7**, an intermediate in the biosynthetic conversion of methionine to ethylene in higher plants, is also known as 2,3-methanoalanine, but it is mostly just called α-ACC or ACC (Figure 4). The α-ACC constituent can also be found in some natural products such as cytotrienins **8**, an apoptosis inducing metabolite isolated from *Streptomyces* species.[8g]

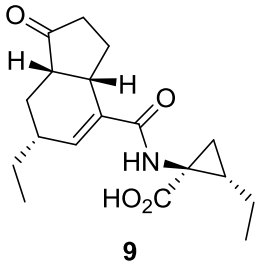


7
1-aminocyclopropanecarboxylic acid (α-ACC)

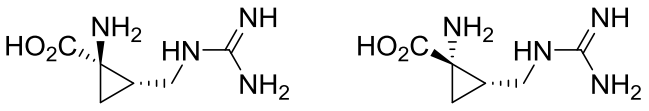
8a (R = 1-cyclohexenyl), cytotrienin A
8b (R = cyclohexyl), cytotrienin B

Figure 4

Generally, related amino acids bearing a cyclopropyl substituent are classified as substituted 1-aminocyclopropanecarboxylic acids. The plant toxin coronatine **9**, produced by *Pseudomonas coronafacience*, is an example of a natural product containing a substituted 2,3-methanoamino acid as constituent (Figure 5).[8e,8g] A naturally occurring 2-aminomethyl-substituted ACC derivative is carnosadine **11**, isolated from the red algae *Grateloupia carnosa*.[8e,8g,16] Replacement of arginine with these 2,3-methano-analogues **10** and **11** leads to peptide conformations with increased stability,[17] whereas spirocyclic peptidomimetics containing these residues tend to preclude ideal bioactive conformations for binding to the vitronectin receptor.[18] Other 2-substituted ACC derivatives also have been incorporated in peptides to study the conformational bias they impart to the peptide chain.[19]



9
coronatine



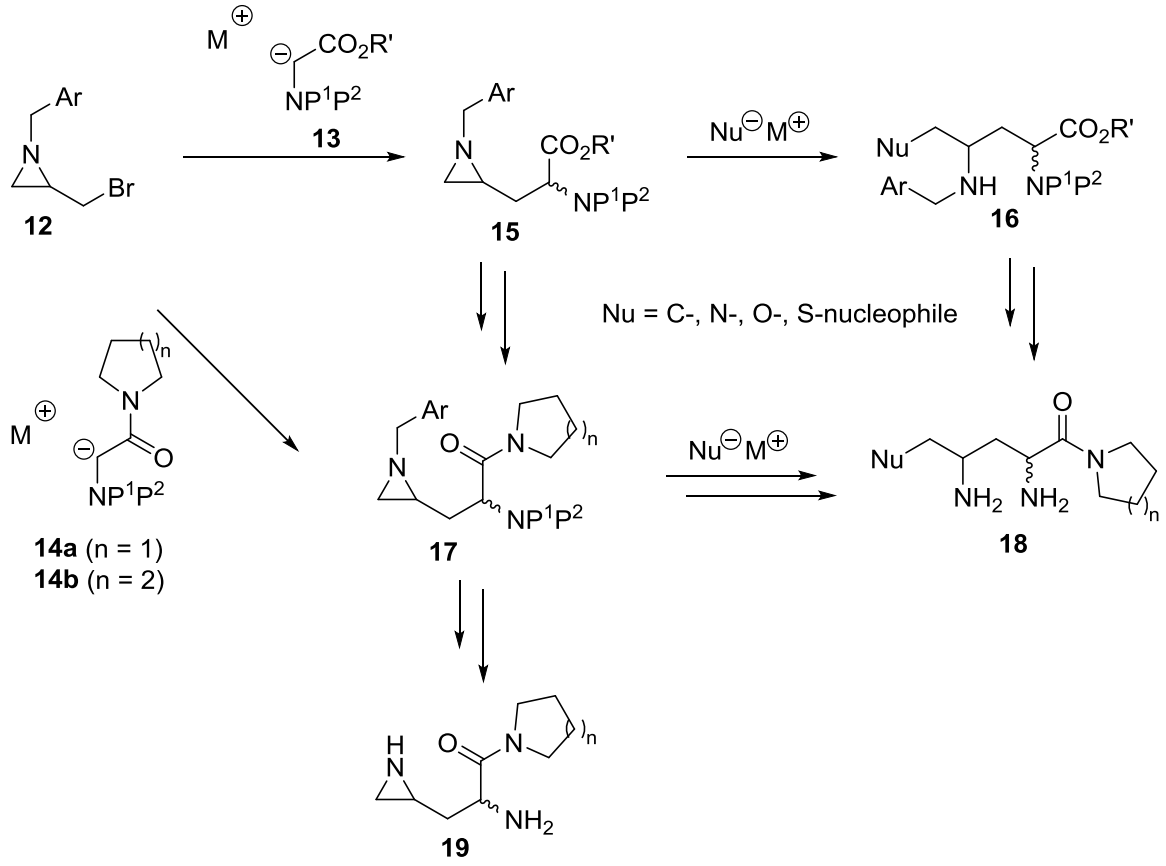
10 **11**
carnosadine

Figure 5

In light of the ubiquitous applications of the above described diamino and conformationally constrained amino acid derivatives as building blocks in organic chemistry and as biologically active

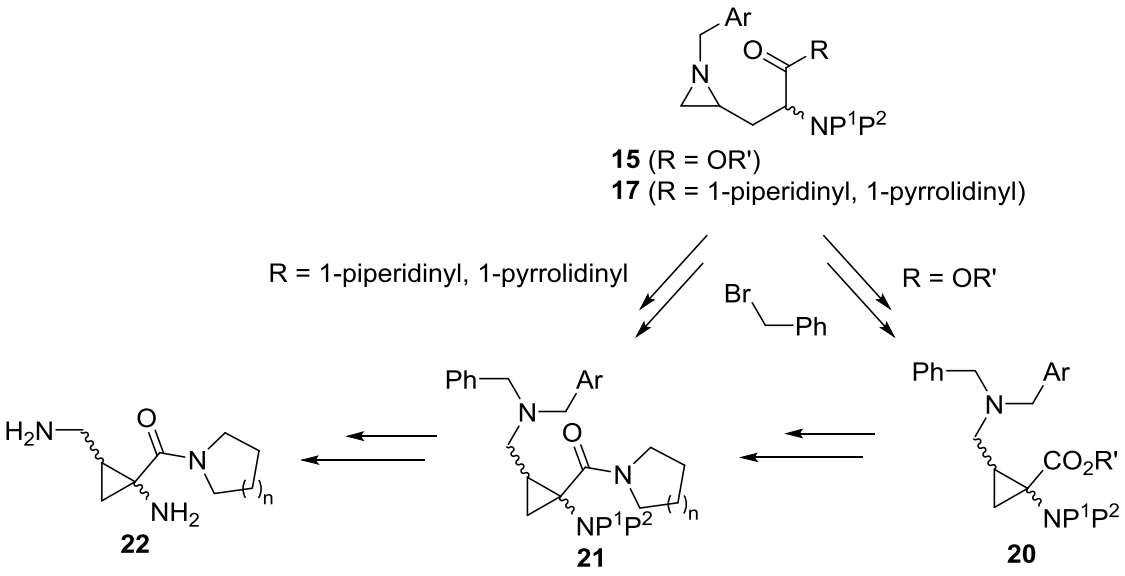
molecules, the synthesis of new representatives of these interesting classes of non-proteinogenic amino acids and their further transformations will be dealt with in this PhD-thesis.

Within a first part of this doctoral study, new synthetic routes towards γ,δ-aziridino α-amino acid derivatives **15** will be developed, starting from aziridines **12**, bearing a functionalized methyl substituent, suitable for nucleophilic substitution, at the 2-position (Scheme 1). Indeed, previous studies at the Department of Sustainable Organic Chemistry and Technology (UGent) have proven that non-activated 2-(bromomethyl)aziridines **12** are valuable synthons for the preparation of a wide variety of azaheterocyclic compounds and ring opened amines.[20] Substitution with deprotonated protected glycine derivatives **13** would give access to 2-(carboxyethyl)aziridines **15** as a new class of conformationally constricted α,γ-diamino acids, which may possess interesting biological activities and could serve as building blocks for a variety of natural products. Indeed, having introduced the 2,4-diaminobutanoyl functionality, these compounds now could serve as scaffolds for the synthesis of new DPP II inhibitors. Ring opening of aziridines **15** with appropriate nucleophiles should lead to amines **16**, which can be further functionalized to the desired potential DPP II inhibitors **18**. In a second approach, amides **18** will be synthesized *via* functionalization of aziridines **15** to the corresponding amides **17**, followed by ring opening. Deprotection of aziridines **17** would lead to the conformationally constrained analogues **19** of Dab-Pip **3**. Finally, γ,δ-aziridino-α-amino amides **17** could be directly obtained *via* nucleophilic substitution of aziridines **12** with deprotonated *N*-protected glycinamides **14**.



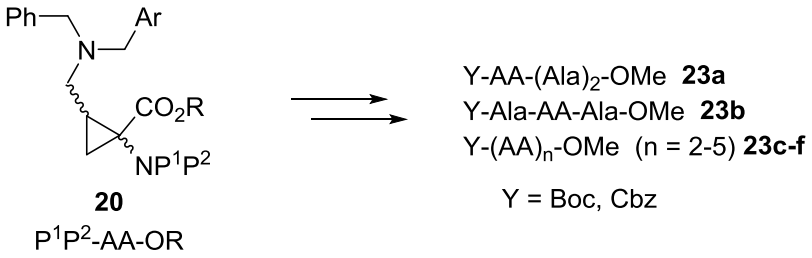
Scheme 1

In a second part of this PhD thesis, the application of constrained γ,δ-aziridino α-amino acid derivatives **15** as synthetic building blocks will be further investigated (Scheme 2). The utility of aziridines as valuable substrates for ring transformation to cyclopropanes has already been demonstrated.[21] Treatment of γ,δ-aziridino α-amino esters **15** with benzyl bromide will allow access to 2-(aminomethyl)-substituted ACC derivatives **20** as precursors for the synthesis of the corresponding amides **21**, which should also be directly available *via* ring transformation of γ,δ-aziridino α-amino amides **17**. Finally, deprotection of cyclopropanes **21** would lead to the 2,3-methano analogues **22** of (*S*)-2,4-diaminobutanoylpiperidine Dab-Pip **3**.



Scheme 2

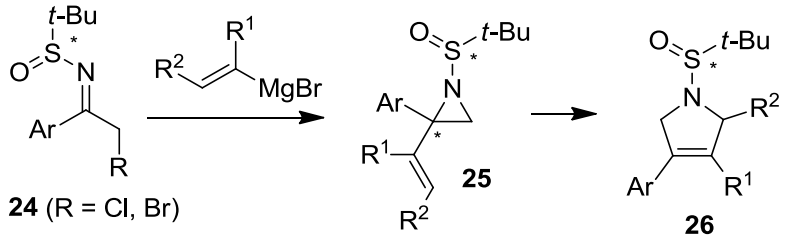
Having the conformationally constrained cyclopropylamino acid derivatives **20** hopefully in hand, these amino acid residues will be incorporated into selected short model peptides **23a,b** containing alanine and homopeptides **23c-f** containing a small number of residues to investigate their conformational preferences and opportunities in the design of peptidomimetic drugs (Scheme 3).



Scheme 3

Within the general objective to synthesize functionalized aziridines as building blocks for a variety of nitrogen-containing compounds, the asymmetric synthesis toward chiral aziridines **25** will be investigated, applying the *tert*-butanesulfinyl group as the chiral directing and protecting group at nitrogen (Scheme 4). Since its introduction by Ellman and co-workers, enantiopure *tert*-butanesulfinamide has been utilized quite extensively in the asymmetric synthesis of a variety of biologically interesting molecules, including amino acid derivatives.[22] The commercially available sulfinamide can be easily used in condensation reactions with aldehydes or ketones. Addition of different nucleophiles across the corresponding imines proceeds with high diastereoselectivities due to the powerful stereodirecting effect of the chiral sulfinyl group. Furthermore, the *tert*-butanesulfinyl group can be selectively deprotected with (dry) HCl.

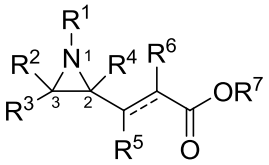
Previous research at the Department of Sustainable Organic Chemistry and Technology (UGent) has shown that reaction of aromatic α-halo *N*-(*tert*-butanesulfinyl)imines **24** with vinylmagnesium bromide resulted *in situ* in *N*-sulfinyl 2-aryl-2-vinylaziridines **25**, which spontaneously rearranged into biologically interesting 3-aryl-3-pyrrolines **26**.[23] The scope of this Grignard addition reaction was extended within a last part of this PhD-thesis and the addition of other alkenylmagnesium bromides was evaluated to verify the possible isolation of 2-alkenylaziridines **25**. Indeed, 2-vinylaziridines and related aziridines have proven to be suitable substrates for transformation into a variety of heterocycles.[24]



Scheme 4

2 Literature overview

Many synthetic strategies for the synthesis of aziridines are described within literature and also in our research group several routes have been developed which include the "De Kimpe aziridine synthesis", starting from α-haloimines and reaction of 2-aza-1,3-dienes with diazomethane.[25] Within this chapter, a literature overview will be given of the main synthetic routes towards 2-(carboxyethyl)aziridines **27** (Figure 6) and, if relevant, their ring transformation into heterocyclic and carbocyclic ring systems such as lactones, lactams, 3-pyrrolines and cyclopropanes. The presence of both the strained aziridine ring system and the functionalized side chain makes these compounds excellent building blocks for the synthesis of many synthetic and natural products of biological importance. A division has been made, based upon the different synthetic approaches towards 2-(carboxyethyl)aziridines, involving different bond connections or functional group transformations. To make a clear distinction between the assignment of absolute and relative stereochemistry, (*R*) or (*S*) were added as stereodescriptors to the stereogenic center in the case of enantiopure compounds. In the case of racemates (±) was added to clarify that the assigned stereochemistry refers to the relative configuration.

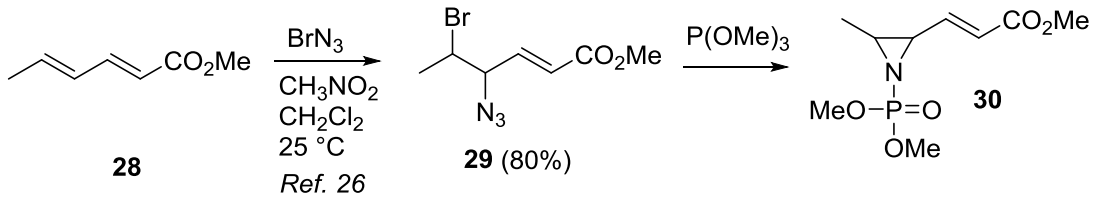


27

Figure 6

2.1 Synthesis of 2-(carboxyethyl)aziridines through N1-C3 bond formation

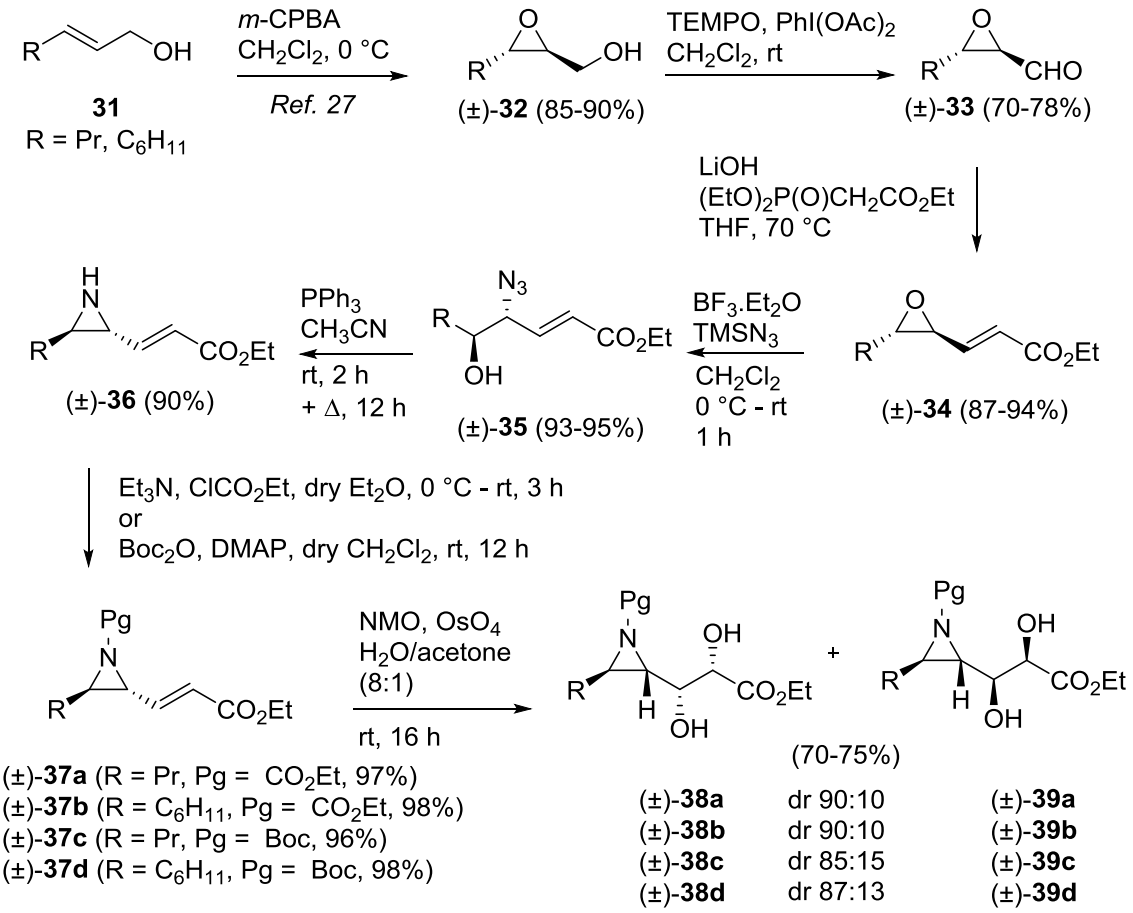
γ-Azido carboxylic acid derivatives bearing a leaving group in the δ-position can easily be transformed into the corresponding aziridines *via* intramolecular nucleophilic substitution. A first example describes the addition of bromine azide to diene **28** to afford brominated azide **29** in 80% yield (Scheme 5). Subsequent ring closure to the corresponding aziridine **30** was performed by treatment of the β-bromoazide **29** with trimethyl phosphite.[26]



28 **29** (80%) **30**

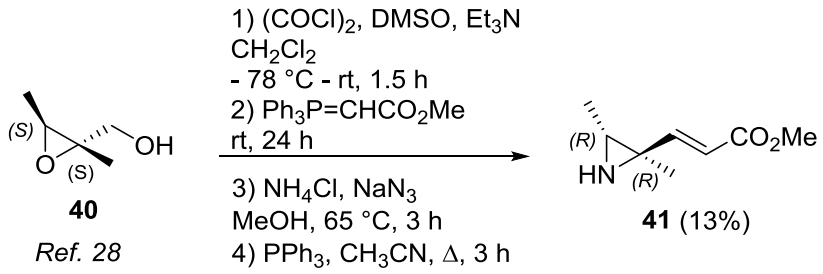
Scheme 5

In a next example, vinylic aziridines (±)-**37** were synthesized, starting from allylic alcohols **31** (Scheme 6).[27] Epoxidation of **31** with *m*-CPBA gave epoxy alcohols (±)-**32**, which were oxidized to the corresponding epoxy aldehydes (±)-**33** using the TEMPO/$PhI(OAc)_2$ method. Subsequent Horner-Wadsworth-Emmons reaction with triethyl phosphonoacetate afforded α,β-unsaturated epoxy esters (±)-**34**, which underwent regio- and stereoselectively ring opening with $TMSN_3$, in the presence of $BF_3.Et_2O$ as Lewis acid. The resulting *anti*-azido alcohols (±)-**35** were ring closed to the corresponding aziridines (±)-**36** *via* a Staudinger reduction. In a final step these aziridines were protected as ethyl and *t*-butyl carbamates (±)-**37**. Stereoselective dihydroxylation of the double bond using OsO_4 yielded diols (±)-**38** and (±)-**39** in 70-75% yield. The presence of the aziridine *N*-protecting group was of utmost importance for the stereochemical control since no stereoselectivity was observed after hydroxylation of the unprotected aziridines (±)-**36** (1:1 mixture of diastereomers).



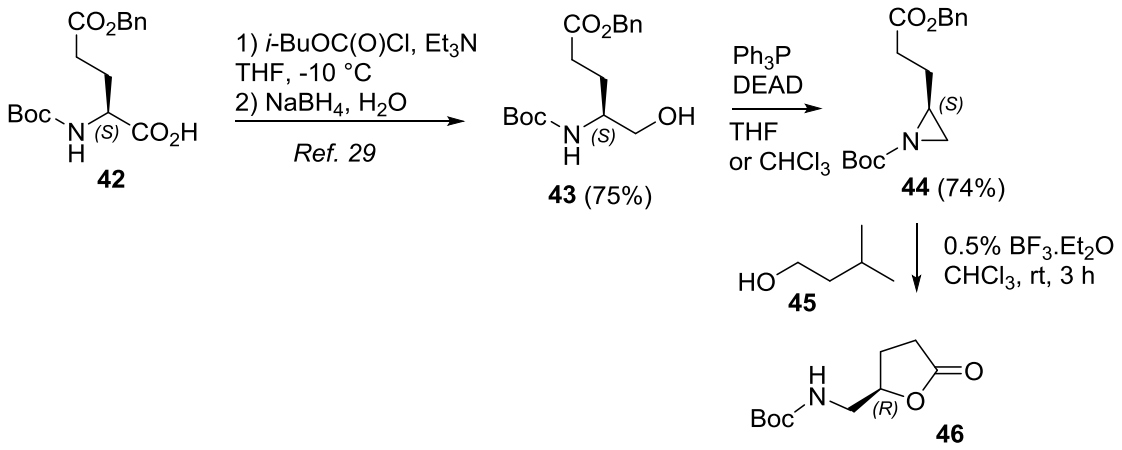
Scheme 6

In a similar way, starting from epoxy alcohol **40**, the synthesis of enantiopure aziridine **41** has been described by Geib and co-workers in 13% overall yield (Scheme 7).[28]



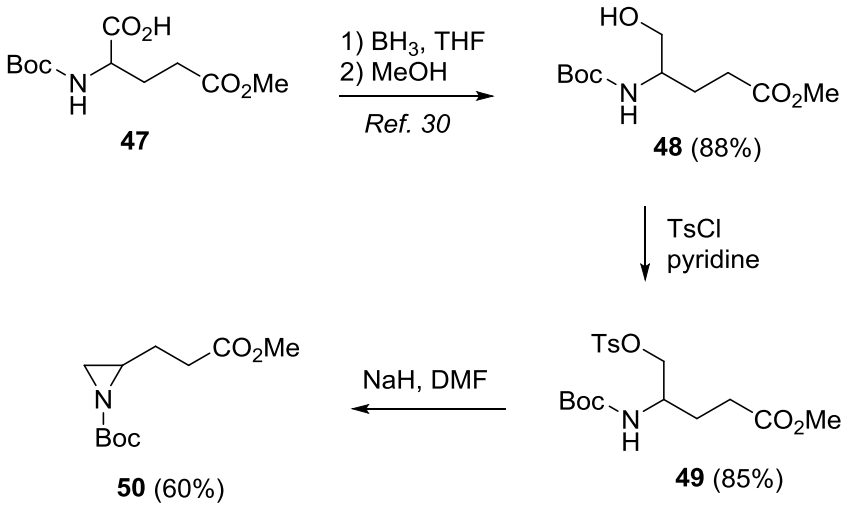
Scheme 7

Another convenient entry towards 2-(carboxyethyl)aziridines starts from *N*-Boc-protected glutamate **42**, which is readily reduced to amino alcohol **43** with sodium borohydride. Cyclization of alcohol **43** under Mitsunobu conditions afforded 2-(carboxyethyl)aziridine **44** in 74% yield (Scheme 8).[29] Subsequent boron(III) fluoride-catalyzed reaction with isoamyl alcohol **45** did not result in the desired ring opening product but instead a ring transformation to γ-lactone **46** was observed.



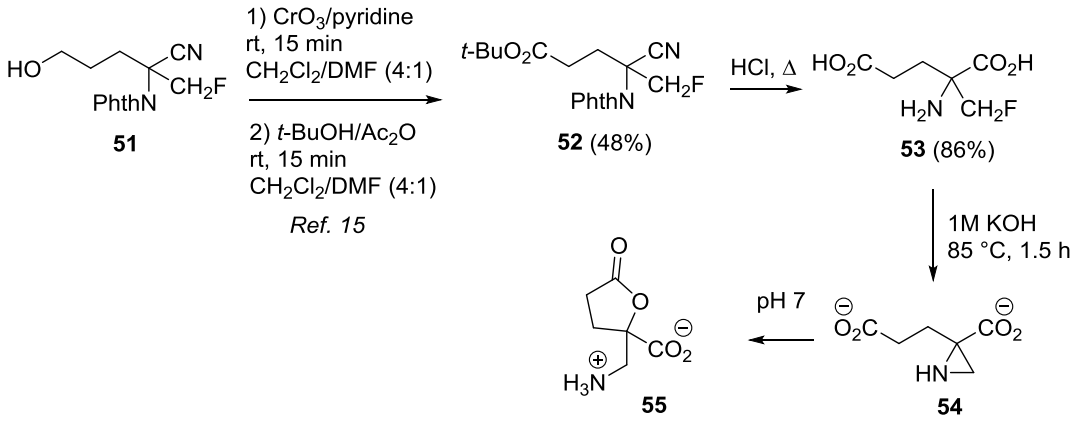
Scheme 8

In another example, Boc-protected glutamic acid δ-methyl ester **47** was reduced with 1M borane in THF to amino alcohol **48**, which was subsequently tosylated in pyridine and ring closed with NaH in DMF to afford aziridine **50** in 60% yield (Scheme 9).[30]



Scheme 9

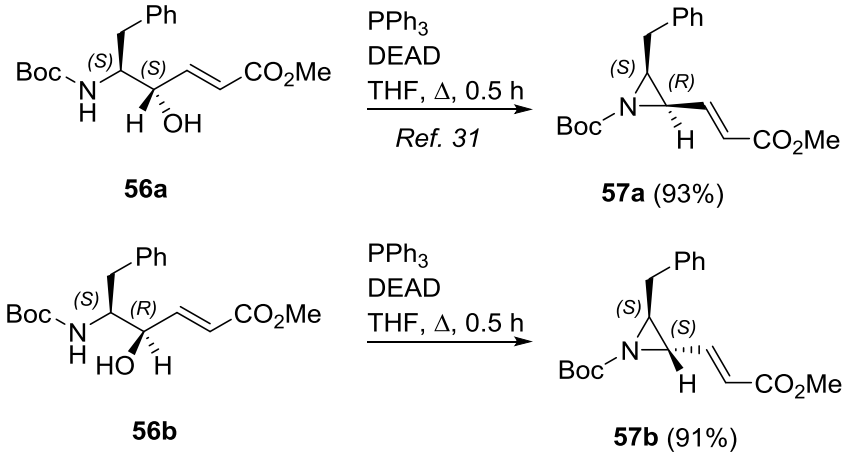
Functionalized alcohol **51**, prepared in three steps from 3-(benzyloxy)propylmagnesium chloride and fluoroacetonitrile, was oxidized with CrO_3/pyridine in the presence of *t*-butanol/acetic anhydride to *t*-butyl ester **52** and subsequent hydrolysis in refluxing HCl afforded racemic α-(fluoromethyl)glutamate **53** in 86% yield (Scheme 10). Finally, aziridino-glutamate **54** was obtained upon heating of acid **53** in 1M KOH at 85 °C. The compound proved to be stable when stored in 1M KOH, however, lowering the pH resulted in cyclization towards γ-lactone **55**. The synthesized analogue of glutamic acid **54** acts as an irreversible inhibitor of *Lactobacillus* glutamate racemase.[15]



Scheme 10

2.2 Synthesis of 2-(carboxyethyl)aziridines through N1-C2 bond formation

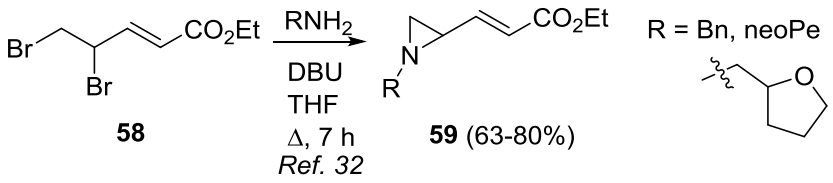
Another example of the use of natural products from the chiral pool for the synthesis of enantiopure 2-(carboxyethyl)aziridines is illustrated by the synthesis of Boc-protected aziridines **57** (Scheme 11). Starting from Boc-protected L-phenylalanine, a six step synthesis afforded both isomers of alcohol **56**, which was ring closed under Mitsunobu conditions to enantiopure aziridines **57a** and **57b** in excellent yield.[31]



Scheme 11

2.3 Synthesis of 2-(carboxyethyl)aziridines *via* the Gabriel-Cromwell reaction

Of several existing aziridination strategies, the Gabriel-Cromwell reaction remains one of the most convenient and useful. Reaction of dibromoester **58** with primary amines in the precense of DBU afforded the corresponding aziridines **59** in 63-80% yield (Scheme 12). The reaction showed to be compatible with a nucleoside-derived amine, which suggests a broad scope of applications, for example as precursor of cofactor mimics of S-adenosyl-L-methionine.[32]

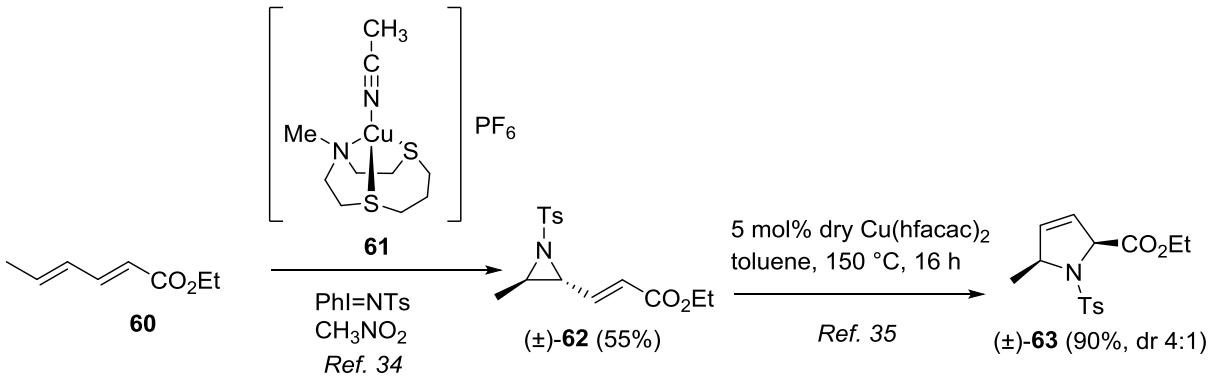


Scheme 12

2.4 Synthesis of 2-(carboxyethyl)aziridines by transfer of nitrogen to olefins

2.4.1 Copper-catalyzed iminoiodinane-mediated aziridination of olefins

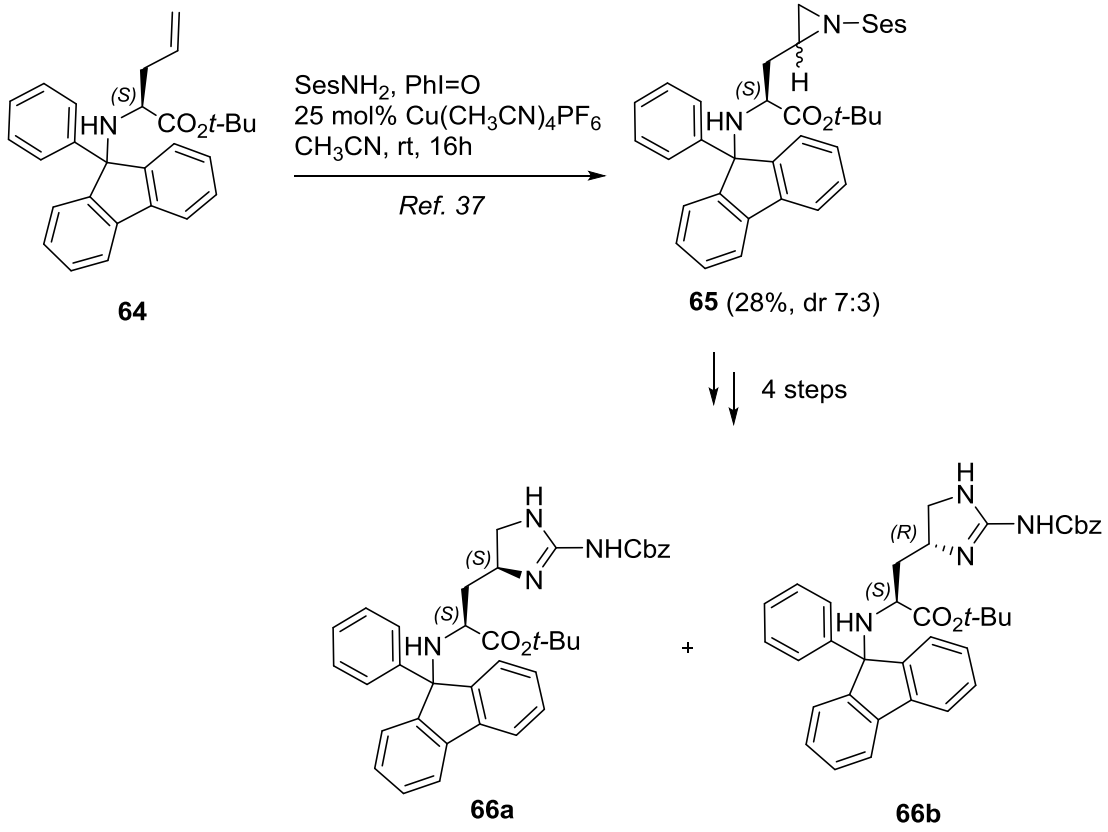
Since its discovery at the end of the 19th century, iodosylbenzene PhI=O is used for the synthesis of epoxides *via* a metal-catalyzed oxygen atom transfer to alkenes. Evans demonstrated that the aza-analogues, i.e. the iminoiodinanes, also react with olefins to give the corresponding aziridines.[33] However, the troublesome preparation of these nitrene sources hampers a wider application of this aziridination process in organic chemistry. A first example describes the aziridination of ethyl sorbate **60** with PhI=NTs as nitrene source, catalyzed by copper-complex **61** (Scheme 13). The system only reacts with the terminal double bond and vinylaziridine (±)-**62** was obtained in 55% yield.[34] Treatment of the latter aziridine with a catalytic amount of copper(II) hexafluoroacetylacetonate in toluene resulted in the diastereoselective formation of 3-pyrroline (±)-**63** in excellent yield.[35]



Scheme 13

A one pot process was developed by Dodd and co-workers, allowing a direct copper-catalyzed nitrogen transfer onto olefins without isolation of these capricious iminoiodinane reagents, mediated by iodosylbenzene itself.[36] In the context of the synthesis of novel conformationally constrained analogues of arginine **66**, one of them being a protected form **66b** of the natural amino acid enduracididine, aziridination of the (*S*)-enantiomer of *N*-phenylfluorenyl (NHPhF) protected allylglycine **64** *via* copper-catalyzed reaction with *in situ* generated PhI=NSes (Ses: $SO_2CH_2CH_2SiMe_3$)

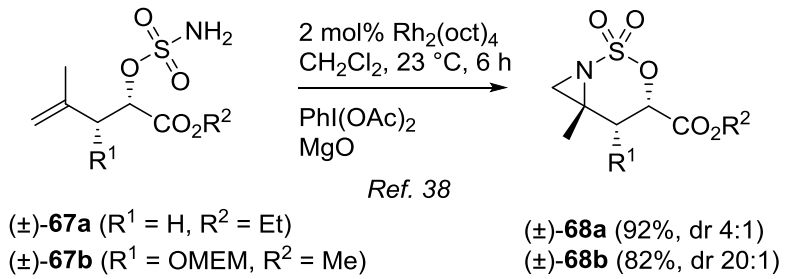
provided an inseparable 7:3 mixture of diastereomers **65** in 28% yield (Scheme 14).[37] An additional four step synthesis afforded the target compounds.



Scheme 14

2.4.2 Rhodium-catalyzed aziridination of sulfamate esters

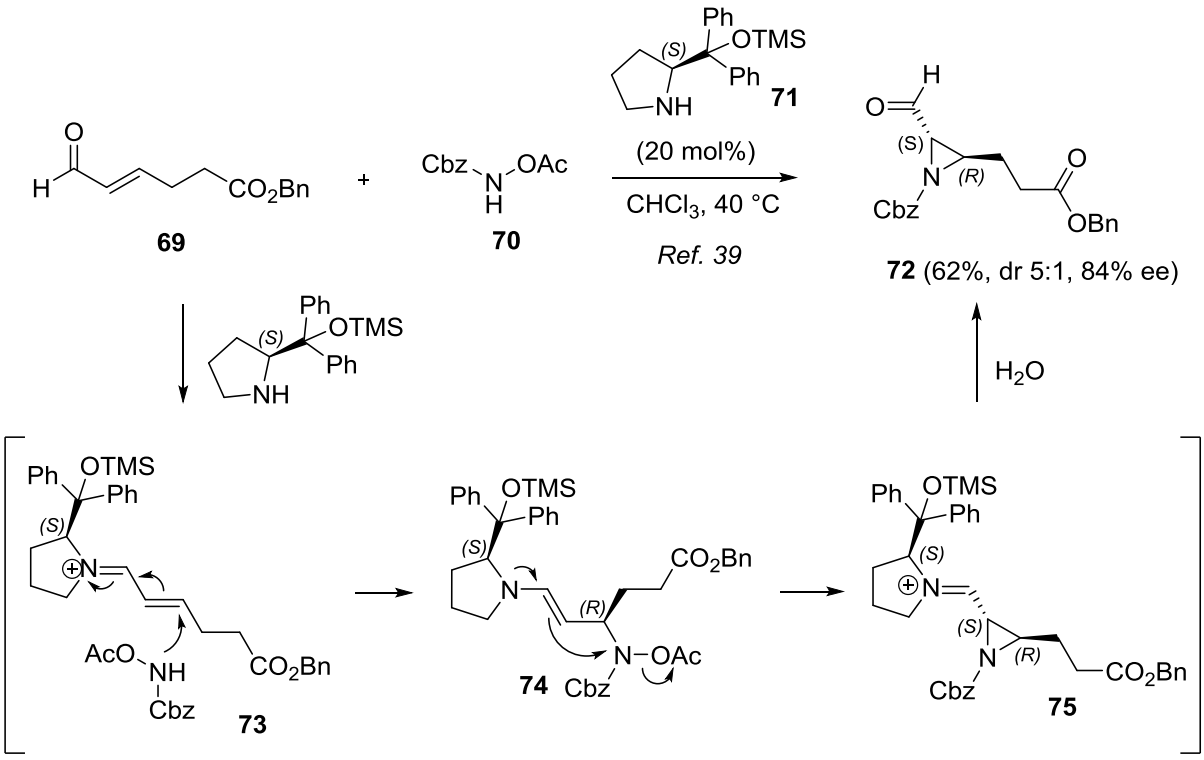
Chiral sulfamate esters (±)-**67** proved to be excellent substrates for a diastereoselective intramolecular aziridination reaction, leading to the corresponding bicyclic aziridines (±)-**68** (Scheme 15).[38] Generation of the active nitrene species was done *in situ* by oxidation of the amine reagent with $PhI(OAc)_2$ in the presence of a catalytic amount of rhodium.



Scheme 15

2.4.3 Aziridination of α,β-unsaturated aldehydes

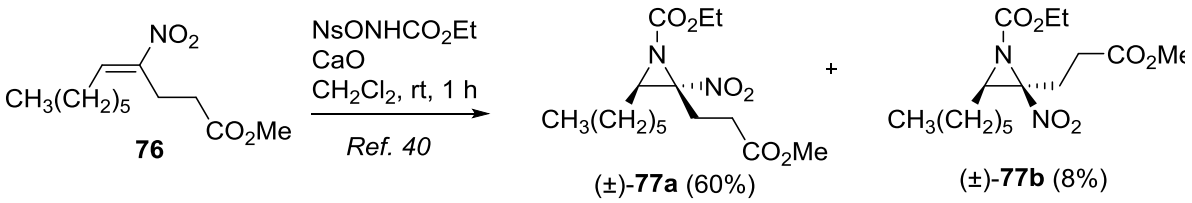
A new highly enantioselective organocatalytic aziridination of α,β-unsaturated aldehydes was described by Córdova en co-workers, involving the formation of catalytic iminium and enamine intermediates (Scheme 16).[39] The formation of 2-(carboxyethyl)aziridine **72** is initiated by reaction of the chiral amine catalyst, TMS-protected diphenylprolinol **71**, with aldehyde **69** to form iminium intermediate **73**. Reaction with acylated hydroxylamine **70** as "nitrene" equivalent *via* an aza-Michael addition gave the corresponding enamine **74**, which is transformed to aziridine **75** *via* enantiocontrolled intramolecular substitution. Finally, the catalyst is regenerated by hydrolysis, delivering 2-formylaziridine **72** in 62% yield.



Scheme 16

2.4.4 Aziridination of nitroalkenes

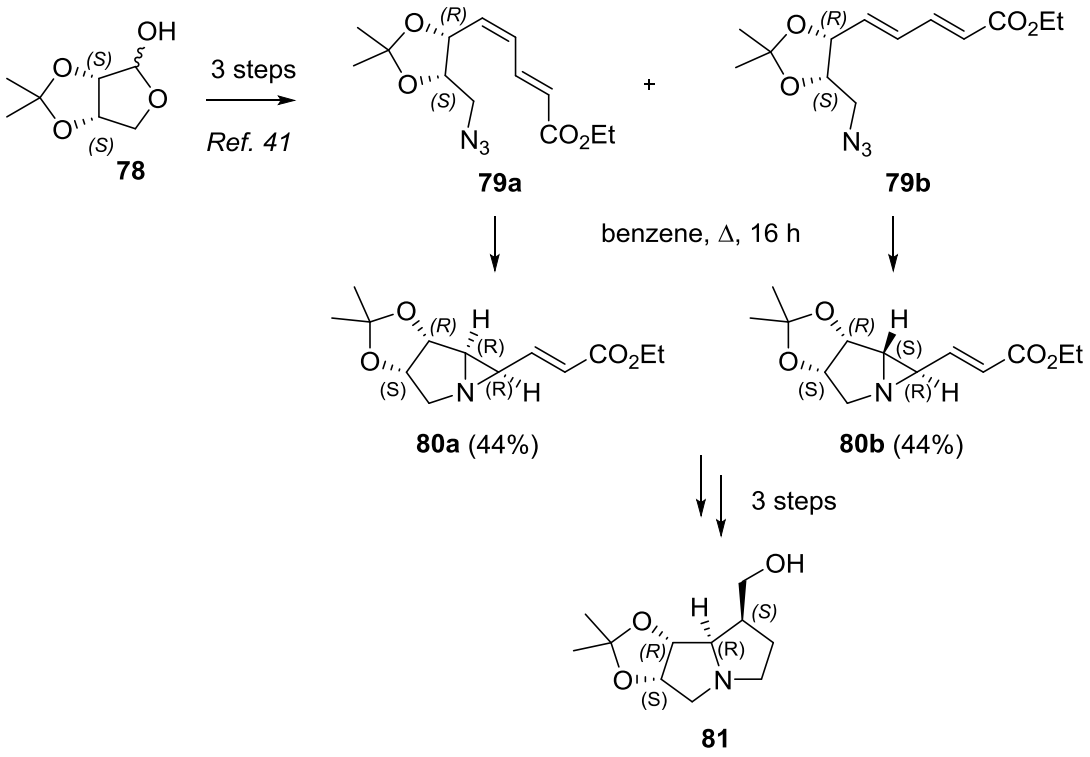
Aziridination of *E*-nitroalkene **76**, using ethyl [(4-nitrobenzenesulfonyl)oxy]carbamate as "nitrene" equivalent in the presence of a base, resulted in the formation of *cis*-aziridine (±)-**77a** as the main product (Scheme 17).[40] Experimental findings suggest that the aziridination proceeds *via* an aza-Michael addition of the $NsON^{-}CO_2Et$ anion to the β-position of the nitro group, followed by ring closure by expulsion of the good leaving group (NsO^{-}) instead of a direct nitrene formation and addition after deprotonation with CaO.



Scheme 17

2.4.5 Aziridination *via* intramolecular azide-diene cycloaddition

Starting from protected L-erythrose **78**, a three step procedure afforded dienes **79**, which were ring closed to the corresponding aziridines upon heating in benzene at reflux *via* intramolecular 1,3-dipolar cycloaddition (Scheme 18).[41] Due to instability of the resulting triazoline intermediates, a thermal rearrangement occurs to the corresponding 2-(carboxyethyl)aziridines **80a,b**. Further elaboration resulted in the synthesis of the pyrrolizidine alkaloid trihydroxyheliotridane as the protected acetonide **81**. Starting from D- erythrose, the other enantiomer was obtained as well.



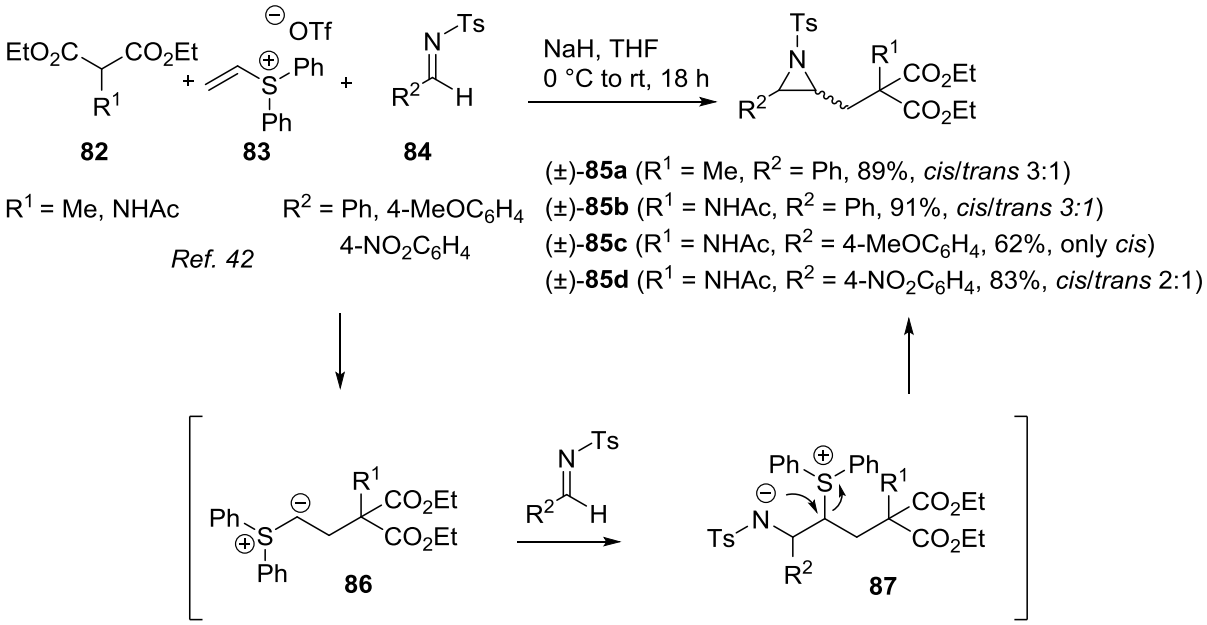
Scheme 18

2.5 Synthesis of 2-(carboxyethyl)aziridines by transfer of carbon to imines

2.5.1 Sulfur ylide-mediated three component aziridination of imines

The application of sulfur ylides in a three-component coupling reaction resulted in the formation of 1-tosyl-2-(carboxyethyl)aziridines (±)-**85** (Scheme 19).[42] Malonate derivatives **82** were deprotonated

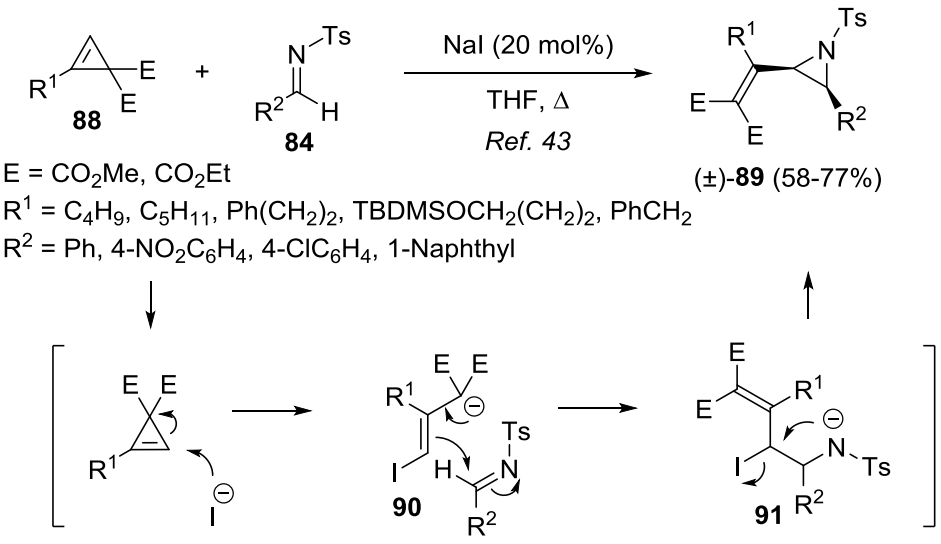
with NaH in THF and reacted with diphenylvinylsulfonium triflate **83**. Addition of the ylide **86** across *N*-tosylimines **84**, followed by intramolecular ring closure, furnished the corresponding *N*-tosyl-2-(carboxyethyl)aziridines (±)-**85** in high yield and moderate *cis*-selectivity, which was improved by using electron-rich aromatic imines. However, the reaction is limited to nucleophiles bearing only one acidic proton. Upon reaction with diethyl malonate (R^1 = H), the electrophilic imine was not trapped and instead a 1,3-proton transfer occurred in the ylide **86**, followed by cyclopropane formation.



Scheme 19

2.5.2 NaI-catalyzed ring opening and aziridination of cyclopropenes with imines

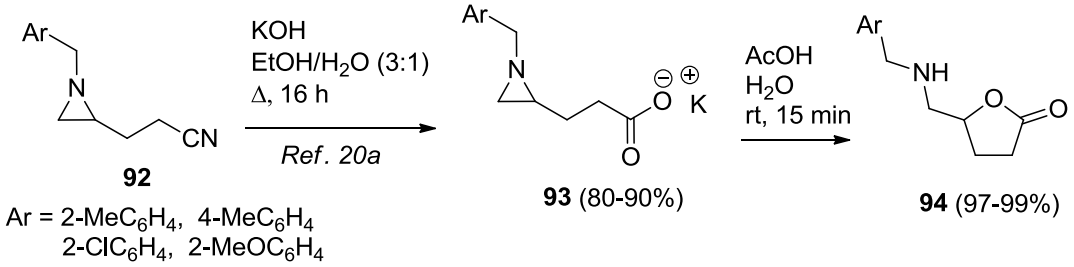
Based upon previous research involving halide-catalyzed ring opening and coupling reactions of cyclopropenes, the group of Hou reported the stereoselective formation of *cis*-vinylaziridines upon NaI-catalyzed reaction of cyclopropenes with imines (Scheme 20).[43] Regioselective ring opening of cyclopropene **88** by the I^- nucleophile leads to the formation of allylic carbanion **90**, which reacts further with *N*-tosylimines **84** to give intermediate **91**. Subsequent intramolecular nucleophilic substitution regenerates I^- and leads to the highly stereoselective formation of *cis*-vinylaziridines (±)-**89** in 58-77% yield. Based upon ^{1}H NMR analysis of the crude reaction mixtures, formation of the *trans*-isomer was not observed.



Scheme 20

2.6 Hydrolysis of 2-(cyanoethyl)aziridines

Treatment of 1-arylmethyl-2-(2-cyanoethyl)aziridines **92**, prepared from 2-(bromomethyl)aziridines, with KOH in EtOH/H_2O (3:1) under reflux afforded the corresponding potassium salts **93** in 80-90% yield (Scheme 21).[20a] Subsequent treatment with acetic acid leads to a ring expansion towards γ-lactones **94** in high yield. Neutralization of the alkaline medium transforms potassium salts **93** into zwitterionic species, which are highly susceptible to ring transformation.



Scheme 21

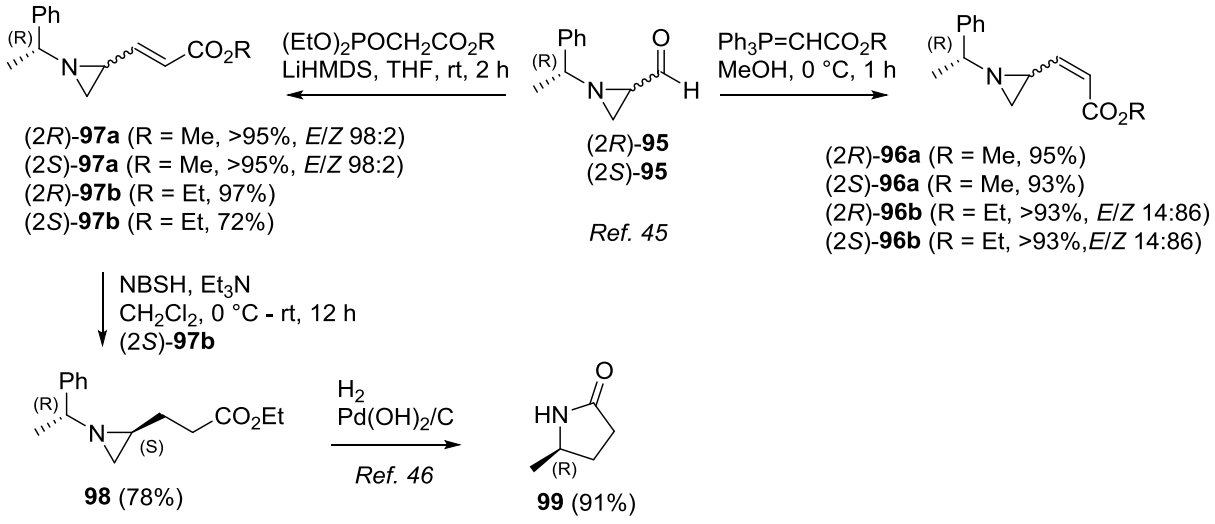
2.7 Functional group transformations towards 2-(carboxyethyl)aziridines starting from aziridine-2-carboxylates or aziridine-2-carboxaldehydes

Several studies have shown the potency of aziridine-2-carboxylates and aziridine-2-carboxaldehydes as synthetic precursors for the synthesis of 2-(carboxyethyl)aziridines via functional group transformations including Wittig or Horner-Wadsworth-Emmons olefination, aldol condensation, condensation with dialkyl malonates, Baylis-Hillman reaction, synthesis of bisaziridines and addition across aldimines.

2.7.1 Synthesis of 2-(carboxyethyl)aziridines *via* Wittig or Horner-Wadsworth-Emmons olefination

A first series of examples starts from chiral *N*-methylbenzyl aziridinecarboxylates or the corresponding aldehydes, easily prepared from commercially available chiral aziridines or upon reaction of 2,3-dibromopropionate with chiral α-methylbenzylamine.[44]

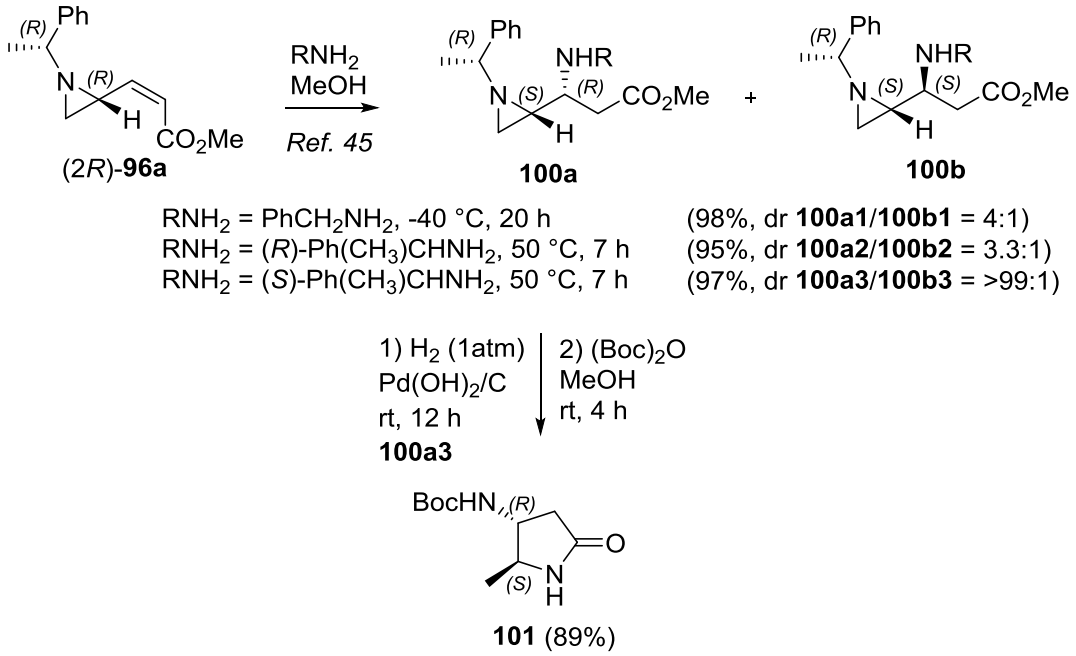
In a first example, enantiomerically pure aziridine-2-carboxaldehydes **95** were prepared *via* oxidation of commercially available alcohols. Wittig-reaction of (2*R*)- and (2*S*)-aziridinecarboxaldehyde **95** with $Ph_3P{=}CHCO_2R$ afforded (2*R*)- and (2*S*)-*Z*-alkenylaziridines **96** in excellent yield and *E*/*Z* ratio. The corresponding *E*-alkenylaziridines **97** were also obtained upon Horner-Wadsworth-Emmons olefination with ethyl and methyl diethyl phosphonoacetate (Scheme 22).[45] Selective reduction of the carbon-carbon double bond of ethyl *E*-(2*S*)-**97b** was achieved upon reaction with *o*-nitrobenzenesulfonylhydrazide (NBSH) in the presence of Et_3N in CH_2Cl_2. The reduction product **98** was hydrogenated with $Pd(OH)_2$/C in a next step to the corresponding (5*R*)-methylpyrrolidin-2-one **99** in 91% yield *via* selective hydrogenolysis of the C(3)-N aziridine bond, debenzylation and subsequent intramolecular cyclization[46].



Scheme 22

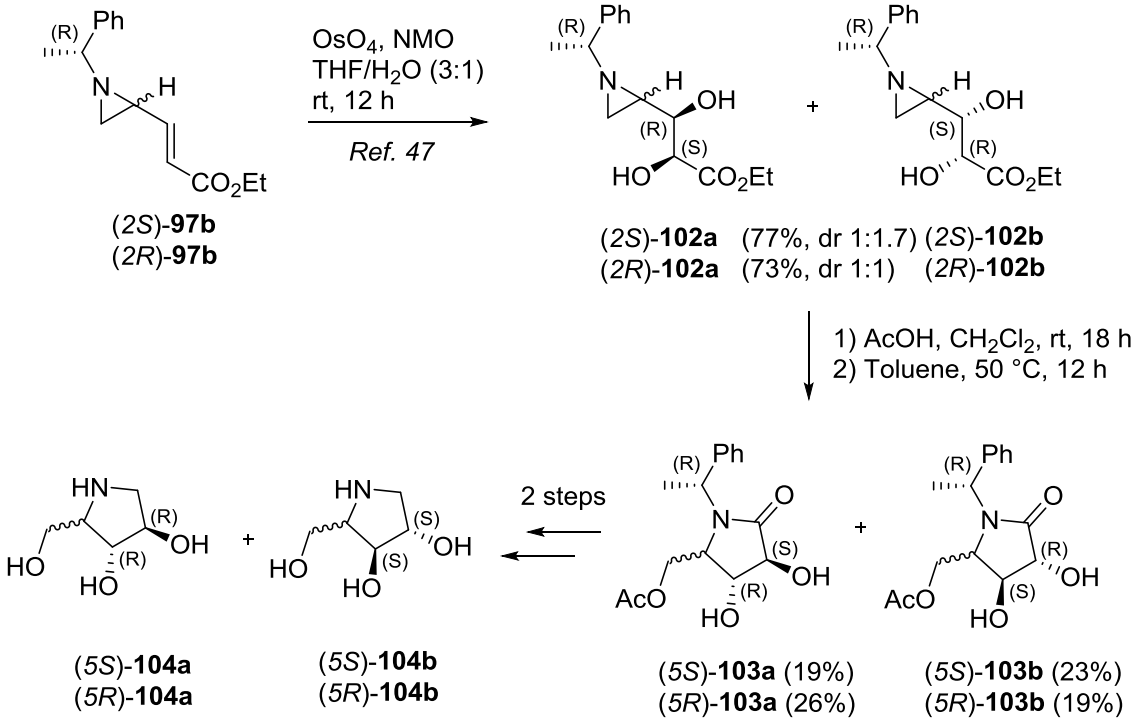
Conjugate addition of benzylamine to methyl *E*- and *Z*-acrylate (2*R*)-**97a** and **96a** showed a big difference in reactivity and stereoselectivity between the two substrates. The *Z*-isomer is much more reactive and led to a diastereomeric mixture of **100a1** and **100b1** in a 4:1 ratio while with the *E*-isomer, the reaction is quite sluggish and no diastereoselectivity was observed (Scheme 23). To improve the diastereoselectivity, the reactions were also performed with (*R*)- and (*S*)-α-methylbenzylamine. In the case of (*R*)-α-methylbenzylamine, no improvement was observed in terms

of selectivity (3.3:1 ratio). However, in the case of the (*S*)-isomer, compound **100a3** was obtained as the only product. The addition of benzylamine to methyl *Z*-(2*S*)-**96a** resulted in a similar selectivity to give addition products in a 2.6:1 ratio. In this case, however, both reactions with (*R*)- and (*S*)-α-methylbenzylamine yielded addition products with poor selectivities of 1.2:1 and 2.1:1, respectively. Finally, addition product **100a3** was cyclized to the Boc-protected γ-lactam **101** upon treatment with hydrogen in the presence of $Pd(OH)_2/C$, followed by reaction with $(Boc)_2O$.



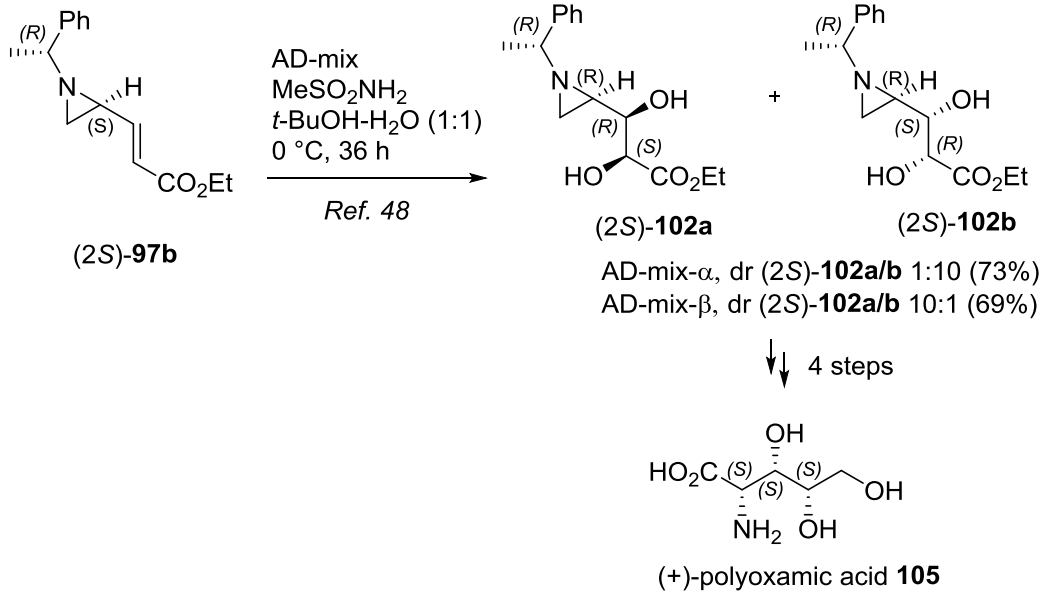
Scheme 23

Cis-dihydroxylation of *E*-enoates (2*S*)- and (2*R*)-**97b** was performed with OsO_4 in the presence of NMO and afforded an inseparable mixture of diastereomers (2*S*)-**102** and (2*R*)-**102** in 77% and 73% yield and diastereomeric ratio of 1:1.7 and 1:1, respectively (Scheme 24).[47] Subsequent treatment with acetic acid in CH_2Cl_2 afforded a regioselective aziridine ring opening, followed by lactamization at 50 °C in toluene to produce a mixture of (5*S*)-**103a-b** and (5*R*)-**103a-b** in the same diastereomeric ratios. This time both diastereomers were separated by facile crystallization. Having the pure diastereomers in hand, they were easily transformed into the corresponding iminosugar 1,4-dideoxy-1,4-imino-D-arabinitol (5*R*)-**104a** and its three stereoisomers in two steps.



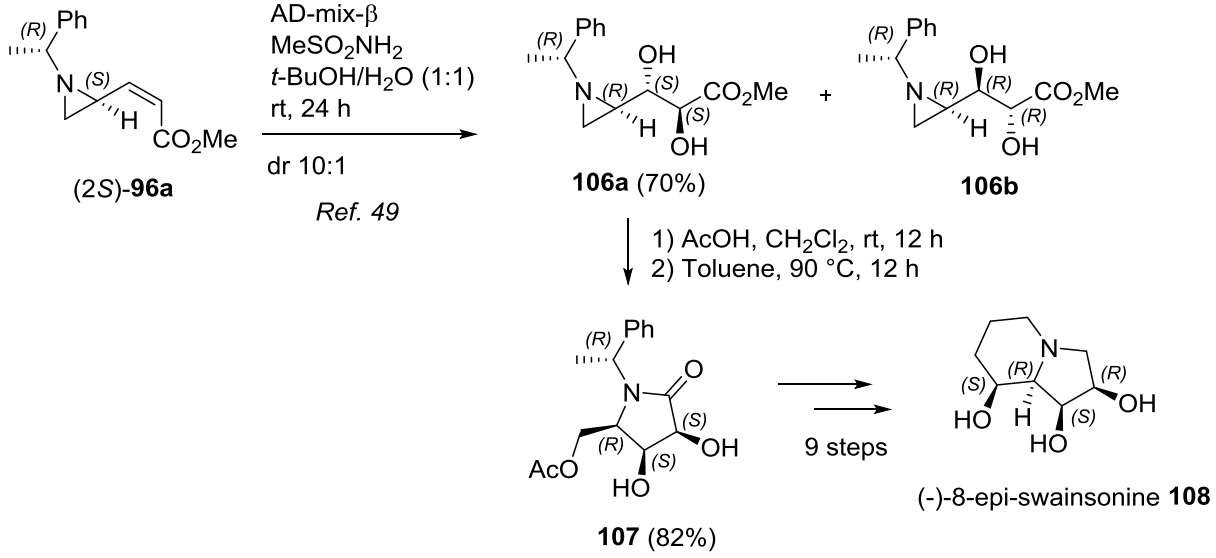
Scheme 24

A higher level of diastereoselectivity was achieved when Sharpless asymmetric dihydroxylation conditions with either the AD-mix-α or AD-mix-β reagents were used. Recently, the synthesis of (+)-polyoxamic acid **105** was described, making use of this stereoselective dihydroxylation step (Scheme 25).[48] (+)-Polyoxamic acid is a polyhydroxy amino acid which is commonly found in a variety of polyoxins, a family of natural peptidyl nucleosidic antibiotics.



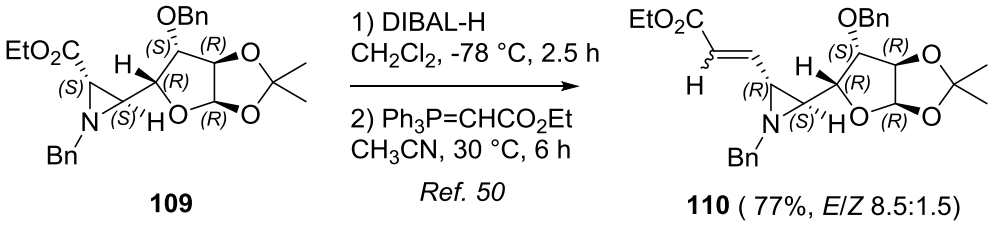
Scheme 25

In a last example, *Z*-enoate (2*S*)-**96a** was subjected to Sharpless asymmetric dihydroxylation using AD-mix-β (Scheme 26).[49] This time (2*S*,3*S*)-2,3-dihydroxy ester **106a** was obtained with a high level of diastereoselectivity (**106a**/**106b** 10:1) and was isolated as a single diastereomer in 70% yield after column chromatography. Again, this diol was transformed into the corresponding γ-lactam **107** in 82% yield. A nine-step synthesis, starting from this lactam afforded the known indolizidine alkaloid (-)-8-epi-swainsonine **108**.



Scheme 26

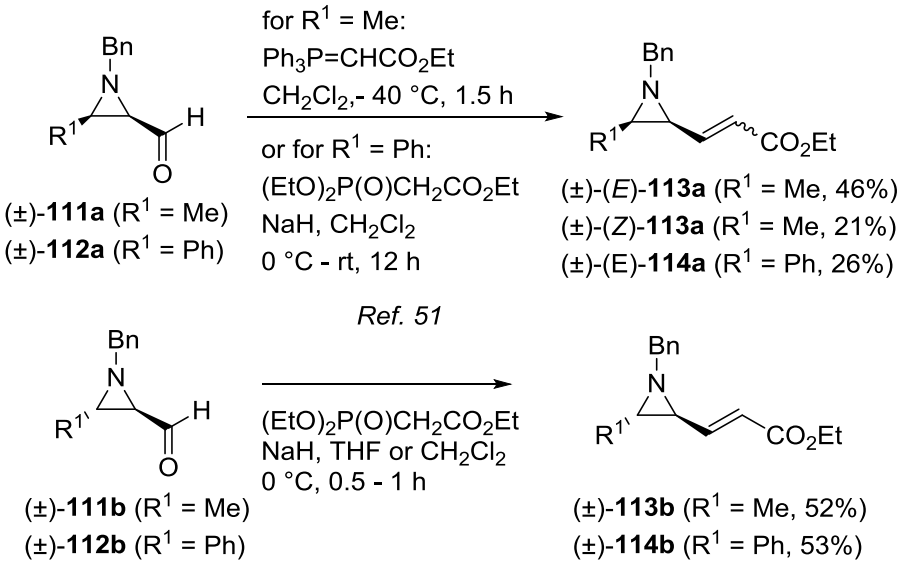
The use of the D-glucose-derived aziridino ester **110**, synthesized from aziridinecarboxylate **109** *via* reduction and subsequent two-carbon homologation using $Ph_3P{=}CHCO_2Et$, has also been described for the preparation of polyhydroxylated quinolizidine and indolizidine alkaloids (Scheme 27).[50]



Scheme 27

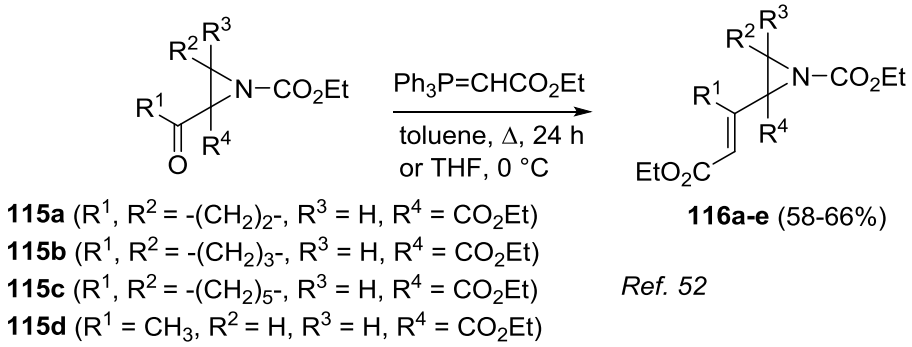
A series of benzyl-protected aziridines (±)-**113** and (±)-**114** was described by Sugiyama and co-workers (Scheme 28).[51] Aldehydes (±)-**111a** and (±)-**111b** were treated with $Ph_3P{=}CHCO_2Et$ or $(EtO)_2P(O)CH_2CO_2Et$, respectively, to afford esters (±)-(*E*)- and (±)-(*Z*)-**113a** in 67% combined yield and (±)-(*E*)-**113b** in 52% yield. In a similar manner, Horner-Wadsworth-Emmons reaction of aldehydes

(±)-**112a** and (±)-**112b** with triethyl phosphonoacetate resulted in the formation of 2-(carboxyethyl)aziridines (±)-**114a** and (±)-**114b** in 26% and 53% yield respectively.



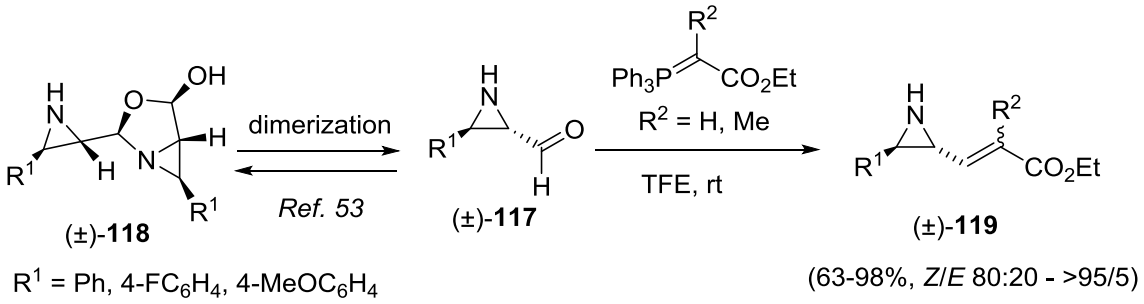
Scheme 28

Tardella and co-workers reported the synthesis of vinyl aziridines **116** *via* wittig olefination with high *E*-stereoselectivity (up to 99%), starting from aziridines **115** (Scheme 29).[52]



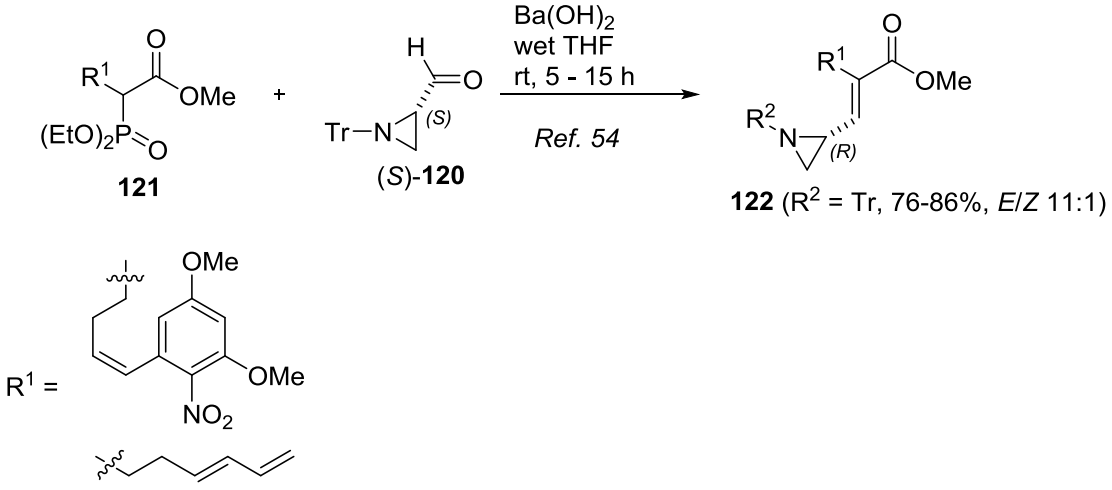
Scheme 29

In a next example, unprotected aziridino aldehydes (±)-**117** were used as starting material. Although these aziridines exist as dimers (±)-**118**, the use of 2,2,2-trifluoroethanol (TFE) as a solvent promotes partial dissociation of the dimer and vinylic aziridines (±)-**119** were obtained in high yield and excellent *Z*-selectivity upon reaction with stabilized Wittig reagents (Scheme 30).[53]



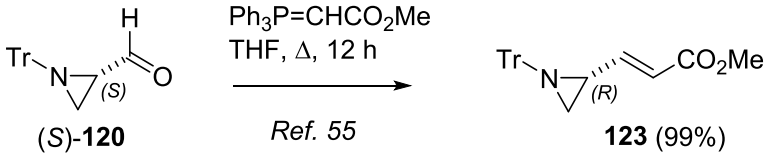
Scheme 30

Several studies have reported the use of (2*S*)-methyl *N*-tritylaziridine-2-carboxylate **124** and (2*S*) *N*-tritylaziridine-2-carboxaldehyde (*S*)-**120**, readily prepared from L-serine, as suitable substrates for the synthesis of 2-(carboxyethyl)aziridines. In a first example, unsaturated esters **122** were prepared as an inseparable *E*/*Z* mixture of isomers (11:1) through a Horner-Wadsworth-Emmons olefination between phosphonate **121** and enantiomerically pure aldehyde (*S*)-**120** (Scheme 31).[54] These scaffolds were used in an efficient approach to the core skeleton of schizozyganes, a small group of hexacyclic indoline alkaloids.



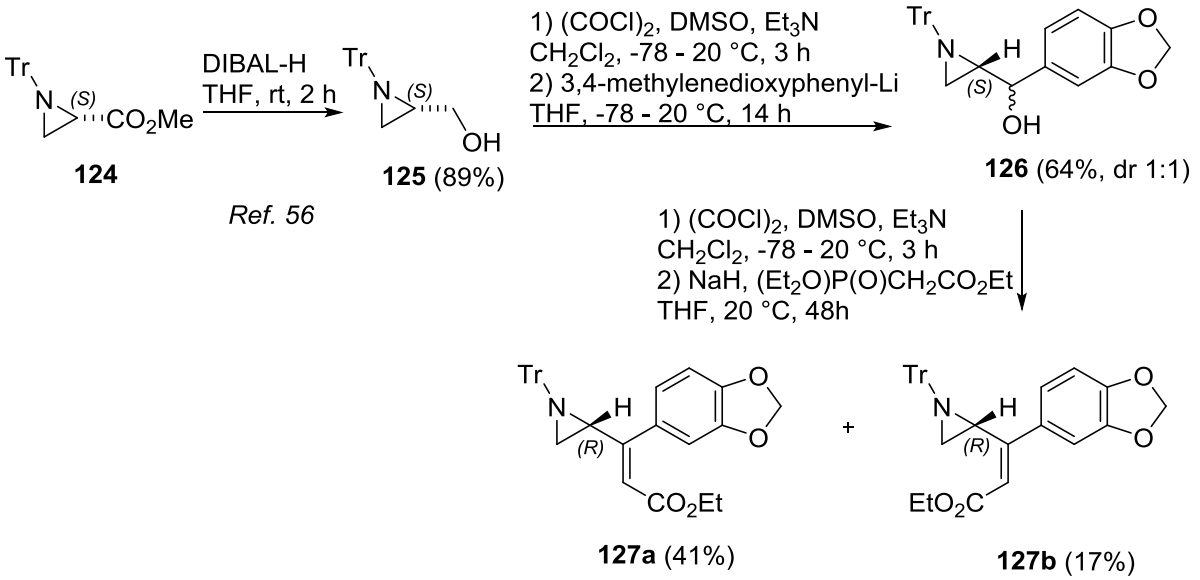
Scheme 31

Homologation of aldehyde (*S*)-**120** *via* Wittig olefination with methyl (triphenylphosphoranylidene)acetate was also possible to yield alkenylaziridine **123** in 99% yield after column chromatography (Scheme 32).[55]



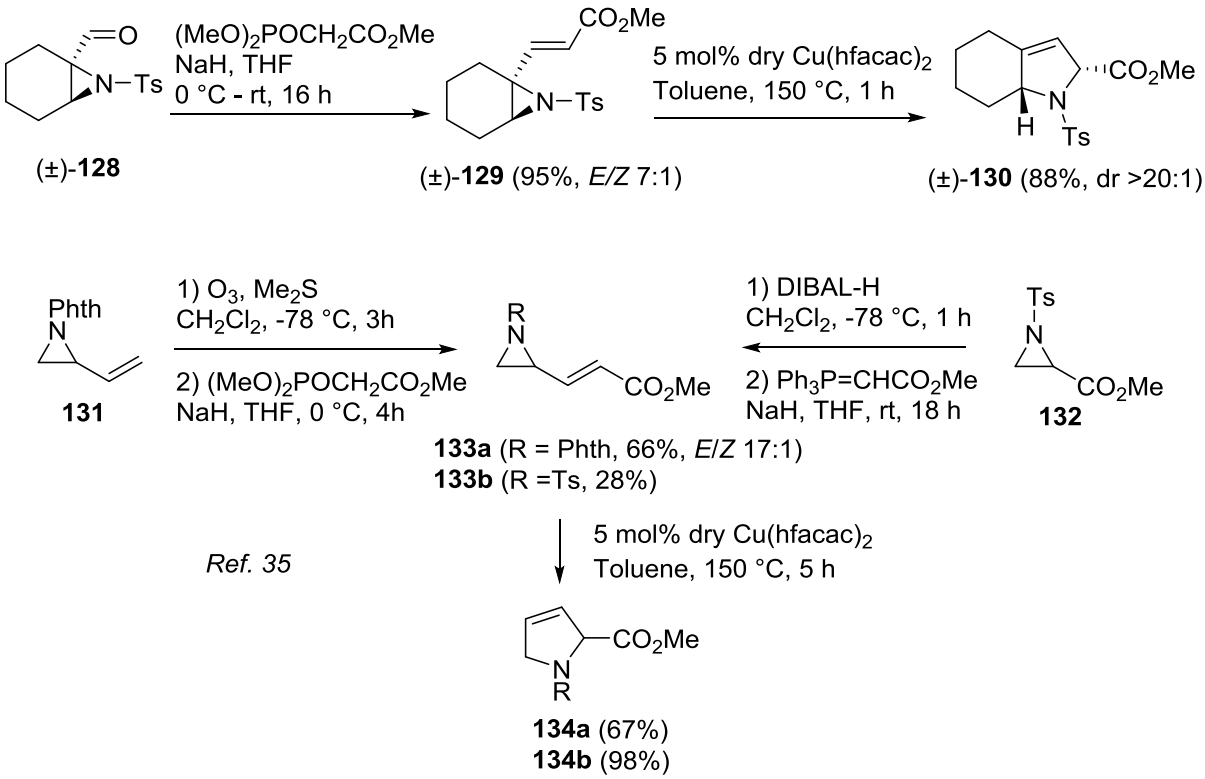
Scheme 32

Another study reports the synthesis of optically active 2-(carboxyethyl)aziridines **127**, starting from (2*S*)-methyl *N*-tritylaziridine-2-carboxylate **124** (Scheme 33).[56] Reduction of the ester with diisobutylaluminium hydride, followed by a Swern oxidation and aryllithium addition resulted in the formation of alcohol **126** in 64% yield as a 1:1 mixture of diastereomers. A second Swern oxidation, followed by Horner olefination gave α,β-unsaturated esters **127a-b** as a mixture of *E*/*Z* isomers, separable *via* column chromatography.



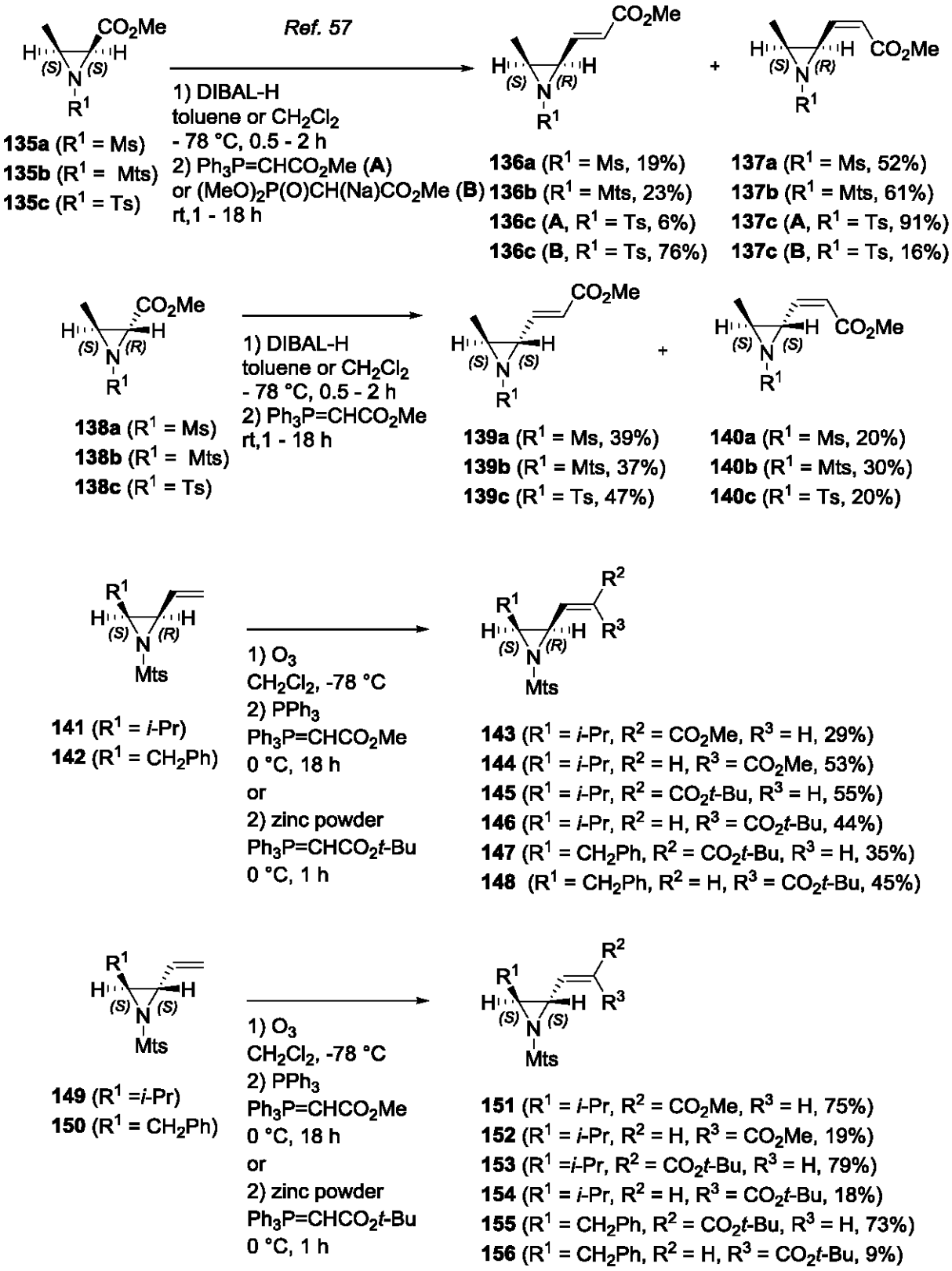
Scheme 33

N-Tosylaziridine (±)-**129** was prepared as a 7:1 *E*/*Z* mixture in 95% yield upon Horner olefination of aldehyde (±)-**128** with trimethyl phosphonoacetate and NaH in THF (Scheme 34).[35] The unsaturated aziridine (±)-**129** was highly diastereoselective rearranged to the corresponding bicyclic 3-pyrroline (±)-**130** using Cu(hfacac)$_2$ as a catalyst. The same study also described the synthesis and copper-catalyzed rearrangement of *N*-phthalimido and *N*-tosyl protected aziridines **133**, obtained *via* Wittig or Horner olefination of the proper starting material **131** or **132**, respectively, to 3-pyrrolines **134**.



Scheme 34

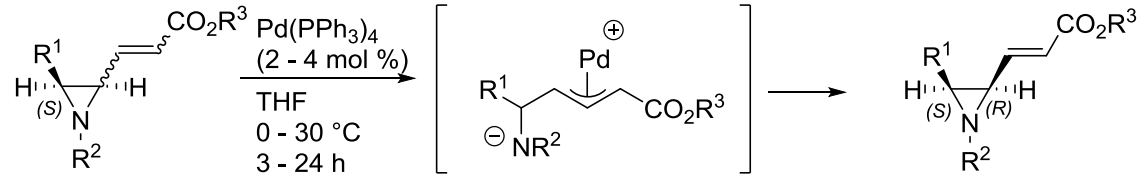
To conclude, a series of optically pure mesyl, tosyl and 2,4,6-trimethylbenzenesulfonyl protected *E*- and *Z*-vinylaziridines were synthesized (Scheme 35).[57] Aziridine-2-carboxylates **135** and **138** and 2-vinylaziridines **141**,**142**,**149** and **150**, prepared from optically active amino acids, amino alcohols or 2,3-epoxy alcohols, were transformed into the corresponding aldehydes *via* reduction with DIBAL-H or ozonolysis, respectively. Wittig olefination afforded separable mixtures of the desired *E*- and *Z*-α,β-unsaturated esters **136**, **137**, **139a,b**, **140**, **143-148** and **151-156**. The sodium salt of trimethyl phosphonoacetate was used to obtain *E*-α,β-enoate **136c** as the major product.



Scheme 35

Theoretical calculations on two sets of four stereoisomeric α,β-enoates (**136a/c**, **137a/c**, **139a/c** and **140a/c**) predicted the order of decreasing relative thermodynamic stabilities to be as follows: 4,5-*cis*-

(2*E*)-**136a/c** > 4,5-*trans*-(2*E*)-**139a/c** > 4,5-*cis*-(2*Z*)-**137a/c** > 4,5-*trans*-(2*Z*)-**140a/c**. These findings were supported by the $Pd(PPh_3)_4$-catalyzed reaction of five sets of four stereoisomeric enoates, (**136a**, **137a**,**139a** or **140a**), (**136b**, **137b**, **139a** or **140a**), (**136c**, **137c**,**139c** or **140c**), (**143**, **144**, **151** or **152**) and (**147**, **148**, **155** of **156**) in THF, leading to equilibrated mixtures of the four possible stereoisomers in which the *cis*-(*E*)-isomers predominated over the others [*cis*-(*E*):other isomers = 85:15−94:6], starting from either isomer (Scheme 36). The stereochemical outcome of these isomerizations was rationalized by considering the formation of π-allylpalladium complexes, generated by oxidative addition to the Pd(0) complex.



(**136a**, **137a**, **139a** or **140a**)
(**136b**, **137b**, **139b** or **140b**)
(**136c**, **137c**, **139c** or **140c**)
(**143**, **144**, **151** or **152**)
(**147**, **148**, **155** or **156**)

(**136a**, **137a**, **139a** and **140a**)
(**136b**, **137b**, **139b** and **140b**)
(**136c**, **137c**, **139c** and **140c**)
(**143**, **144**, **151** and **152**)
(**147**, **148**, **155** and **156**)

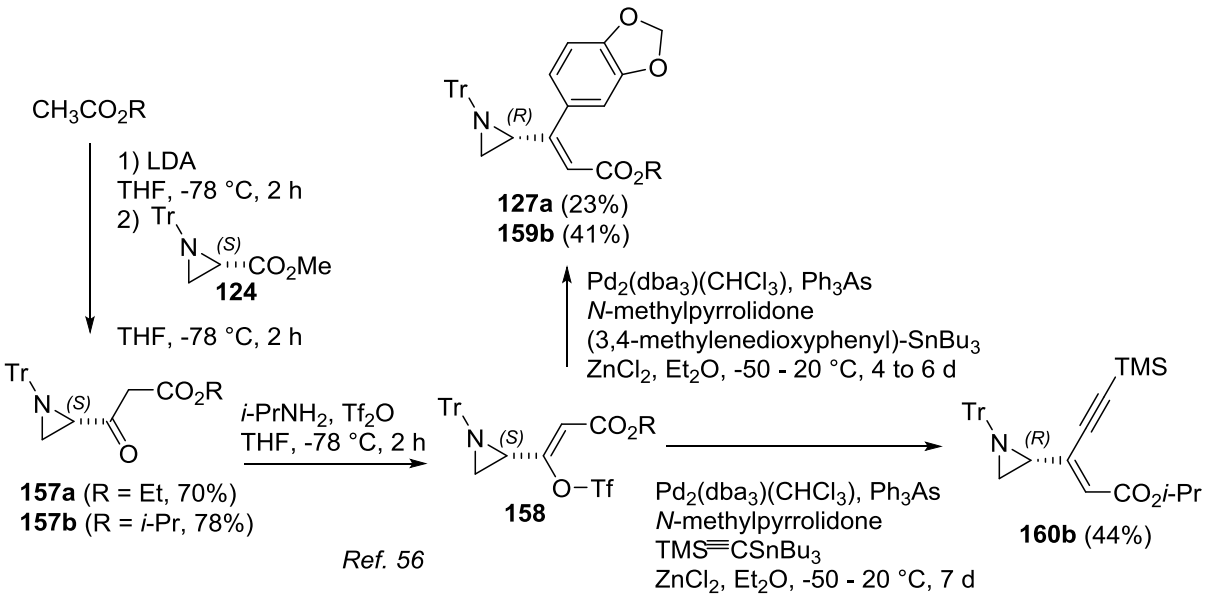
Ref. 57

cis-(*E*)-**136a**
cis-(*E*)-**136b**
cis-(*E*)-**136c**
cis-(*E*)-**143**
cis-(*E*)-**147**
(58 - 98%)
(dr 85:15 - 94:6)

Scheme 36

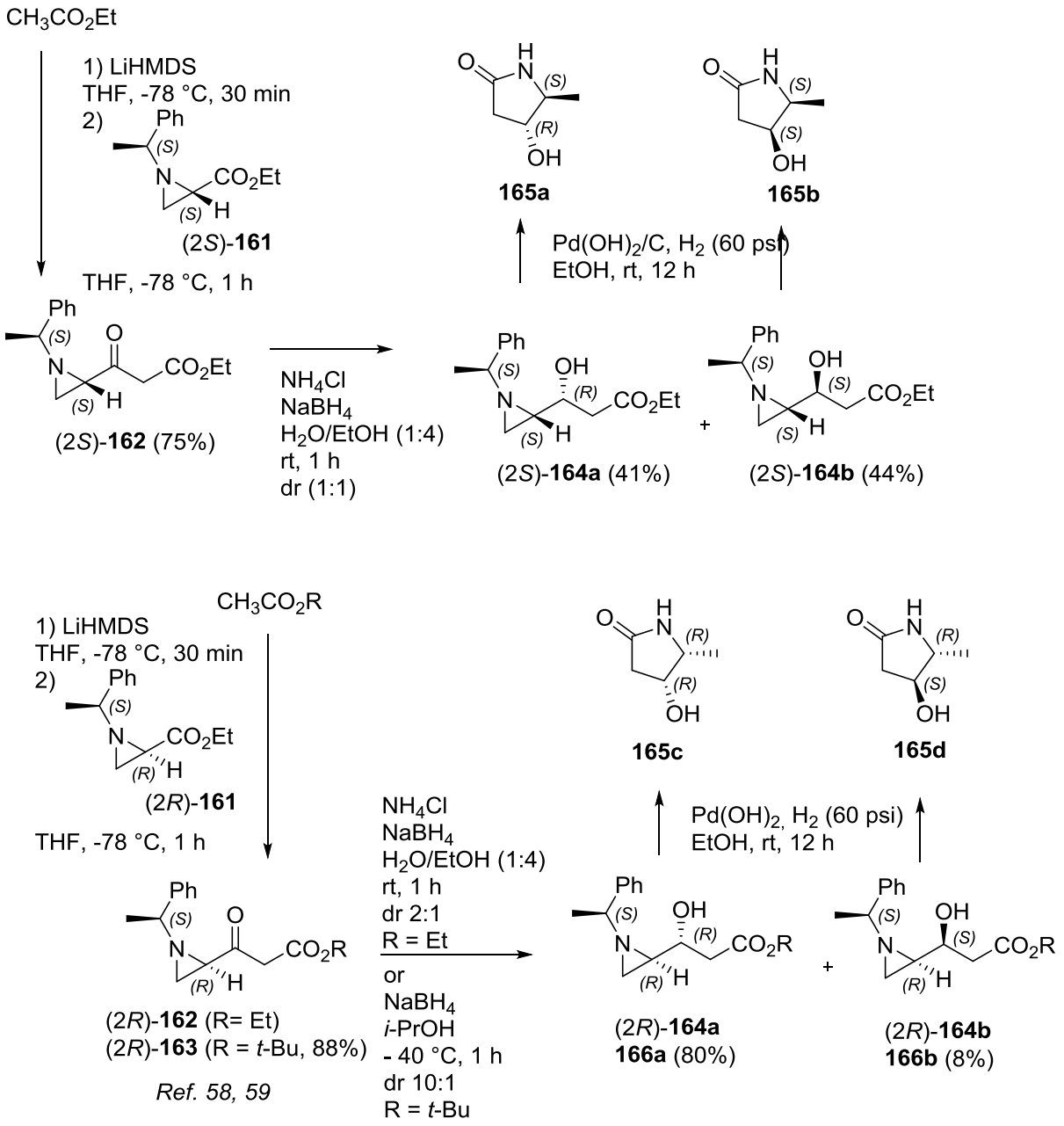
2.7.2 Synthesis of 2-(carboxyethyl)aziridines *via* the aldol condensation

β-Keto esters **157** were prepared *via* a Claisen condensation of aziridino ester **124** with the enolate of *i*-propyl and ethyl acetate (Scheme 37).[56] The conversion of these β-keto esters **157** to α,β-unsaturated esters *E*-**127a**, **159b** and **160b**, bearing an additional aryl or alkynyl substituent *cis* with respect to the ester group, was achieved upon *in situ* generation of enol triflates **158** followed by Pd-catalyzed Stille cross-coupling reactions.



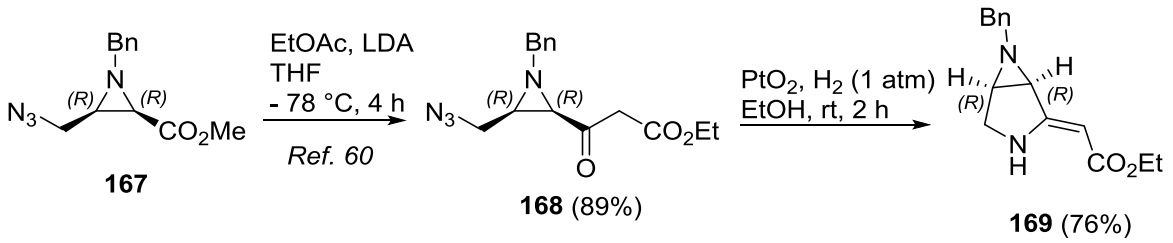
Scheme 37

In another example, enantiomerically pure aziridino ethyl esters **161** were transformed into the corresponding β-keto esters **162** upon homologation with the enolate of ethyl acetate, obtained after deprotonation with LiHMDS in THF. Reduction of the latter compounds with $NaBH_4$ in the presence of NH_4Cl, led to a 1:1 and 2:1 diastereomeric mixture of aziridino alcohols (2*S*)-**164a-b** and (2*R*)-**164a-b** respectively, separable *via* column chromatography (Scheme 38).[58] Reaction conditions were not further optimized to obtain a higher stereoselectivity. Hydrogenation with $Pd(OH)_2/C$ resulted in debenzylation and ring transformation to 5-methyl-4-hydroxypyrrolidinones **165a-d**. These pyrrolidinones were further transformed into the 5-methyl-4-mercapto analogues and used for the synthesis of a new series of 1β-methylcarbapenems, showing excellent antibacterial activity. In another study, reaction of chiral aziridino ethyl ester (2*R*)-**161** with *t*-butyl acetate yielded β-keto ester (2*R*)-**163** in 88% yield (Scheme 38).[59] This time, the reaction conditions were optimized to reduce the latter compound with high stereoselectivity. Sodium borohydride in isopropyl alcohol at -40 °C provided the best result and diastereomers **166a-b** were obtained as a 10:1 mixture in 88% yield.



Scheme 38

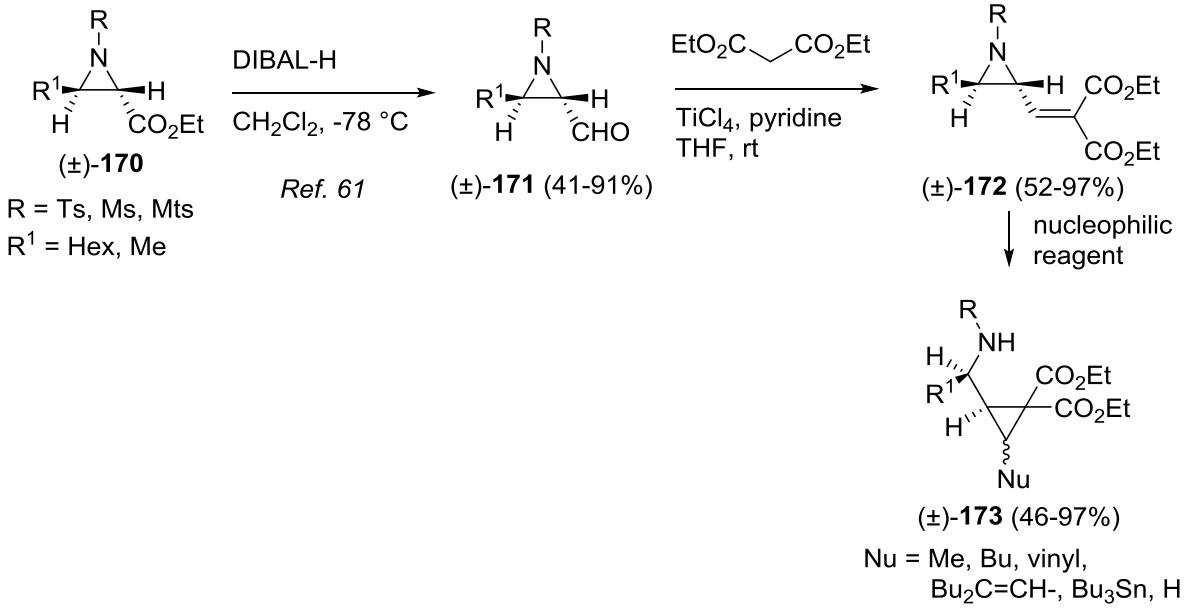
In a final example, methyl 3-(azidomethyl)aziridine-2-carboxylate **167**, synthesized from vinylglycine in six steps, was converted to β-keto ester **168** upon reaction with the enolate of ethyl acetate, generated with LDA in THF. Reduction of the azide afforded bicyclic aziridine **169** in 76% yield (Scheme 39).[60] This aziridinopyrrolidine was used as a building block for the synthesis of analogues of mitomycin antitumor antibiotics.



Scheme 39

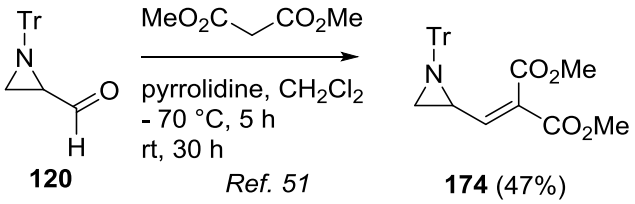
2.7.3 Synthesis of 2-(carboxyethyl)aziridines *via* condensation with dialkyl malonates

Racemic aziridines (±)-**170** were reduced with DIBAL-H to aldehydes (±)-**171**, followed by condensation with diethyl malonate to afford alkenyl aziridines (±)-**172**, which were suitable substrates for a Michael-initiated ring closure (MIRC) reaction with a series of organometallic reagents (Scheme 40).[61] A variety of substituents were introduced onto the resulting cyclopropanedicarboxylic ester derivatives (±)-**173** with highly diastereoselective formation of the *cis*-isomer (*cis*/*trans* ratios ranged from 1:1 to 91:9).



Scheme 40

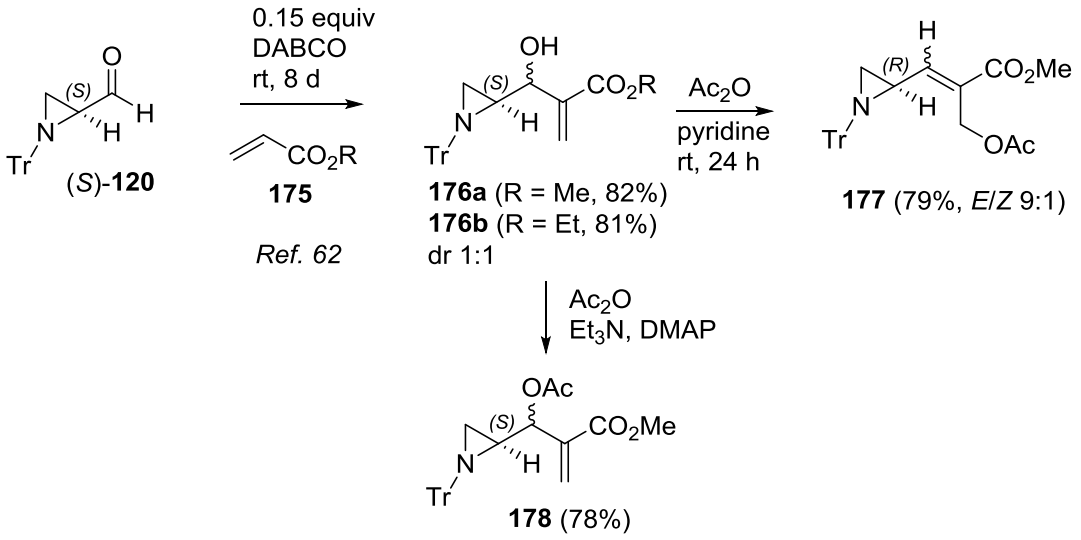
A second example describes the reaction of *N*-tritylaziridine-2-carboxaldehyde **120** with dimethyl malonate to afford diester **174** in 47% yield (Scheme 41).[51]



Scheme 41

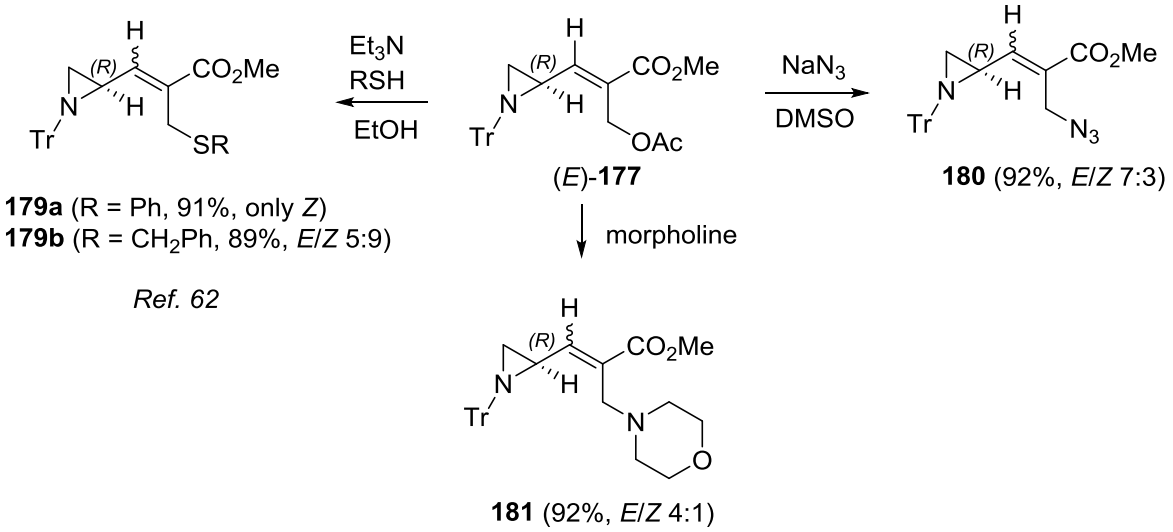
2.7.4 Synthesis of 2-(carboxyethyl)aziridines *via* the Baylis-Hillman reaction

N-tritylaziridine-(2*S*)-carboxaldehyde **120** undergoes facile Baylis-Hillman reaction with activated alkenes **175**, resulting in a separable 1:1 mixture of the *syn*- and *anti*-adducts **176** (Scheme 42).[62] The synthetic utility of these adducts was further investigated and acetylation of **176a** with Ac_2O/Et_3N gave acetate **178** in good yield. However, when Ac_2O/pyridine was used instead, the rearranged acetate **177** was obtained, the *E*-isomer being the main product. The thermodynamically more stable trisubstituted alkene **177** is obtained *via* a S_N2' substitution of the allylic acetate **178** by acetate.



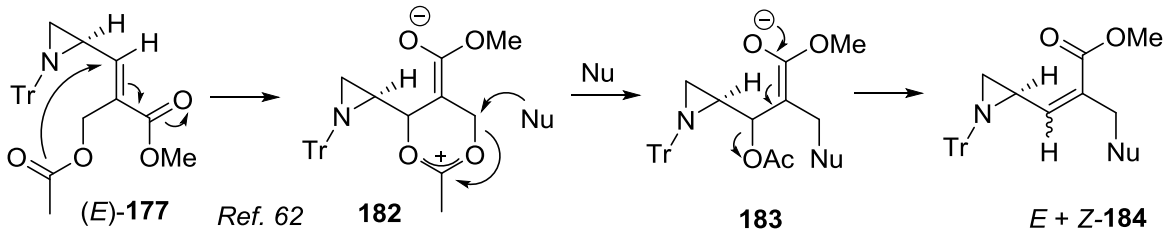
Scheme 42

Treatment of (*E)*-**177** with various nucleophiles resulted in the apparent S_N2 substitution products **179-181** as the sole regioisomers (Scheme 43).



Scheme 43

Remarkably, these compounds were obtained as a mixture of *E*- and *Z*-isomers, which is not in accordance with a direct S_N2 displacement.[62] This result could be explained by the initial formation of an ionic intermediate **182**, followed by reaction with the nucleophile to give intermediate **183** and expulsion of acetate to give a mixture of *E*- and *Z*-isomers **184** (Scheme 44).

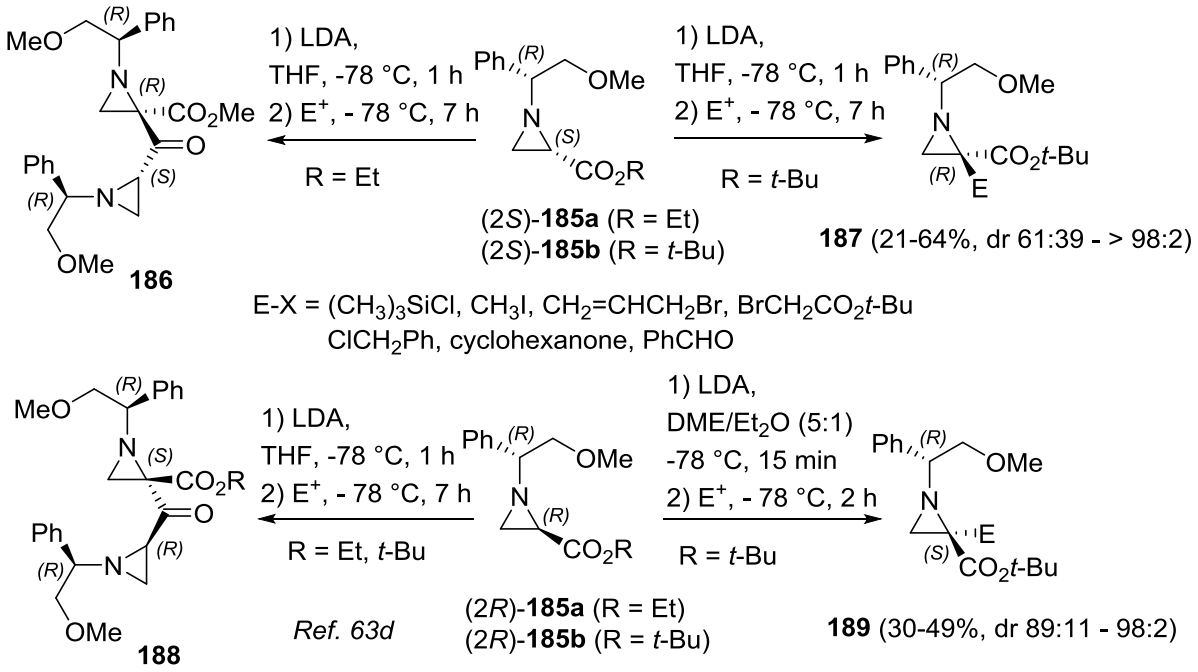


Scheme 44

2.7.5 Synthesis of bisaziridines

Alkylation of aziridine-2-carboxylates has been proven to be difficult due to either degradation or self-condensation of the resulting enolate species after deprotonation with LDA. Indeed several studies report the formation of bisaziridines as the main condensation product.[63] For example, aziridino ethyl ester (2*S*)-**185a** was deprotonated with LDA in THF at -78 °C and subsequent reaction with an electrophile afforded condensation product **186** (Scheme 45).[63d] The *t*-butyl ester (2*S*)-**185b**, however, was deprotonated and reacted with different electrophiles under the same conditions to give aziridines **187**. When the same reaction conditions were used on aziridino esters (2*R*)-**185**, again only aziridinyl ketones **188** were isolated. In contrast, in a 5:1 mixture of DME/Et_2O, the aziridine (2*R*)-**185b** was functionalized to aziridines **189** in moderate yields. However, competitive self-condensation could not be completely avoided. Due to steric reasons, stabilization of the transition

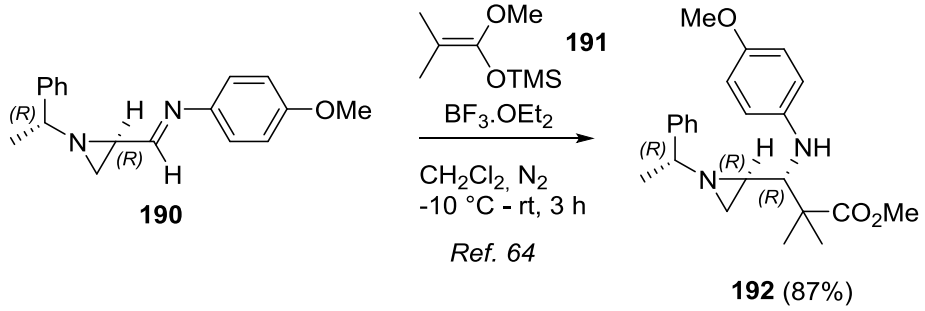
state does not occur for diastereomer (2*R*)-**185b**, and an intermolecular stabilization by DME is required.



Scheme 45

2.7.6 Synthesis of 2-(carboxyethyl)aziridines *via* addition across aldimines

Enantiopure diamine **192** was constructed upon addition of ketene silyl acetal **191** across chiral aziridinyl-2-carboxaldimine **190**, prepared from the condensation of carboxaldehyde (2*R*)-**95** with *p*-anisidine, in the presence of $BF_3.OEt_2$ as a single diastereomer in 87% yield (Scheme 46).[64]



Scheme 46

2.8 Conclusion

In conclusion, it can be stated that many different approaches towards stereochemically defined 2-(carboxyethyl)aziridines have been reported in literature with diverse substitution patterns. As demonstrated in this overview, the presence of the strained ring system and the functionalized side

chain makes these substrates excellent building blocks for a variety of natural products. However, only one synthesis has been reported to date (see section 2.4.1) leading to 2-(carboxyethyl)aziridines bearing an amino substituent at the α-position of the ester moiety and therefore new approaches towards these γ,δ-aziridino α-amino acid derivatives, which is envisioned within this research, might be a valuable addition to this class of attractive substrates as synthetic building blocks.

3 Results and discussion

3.1 Introduction

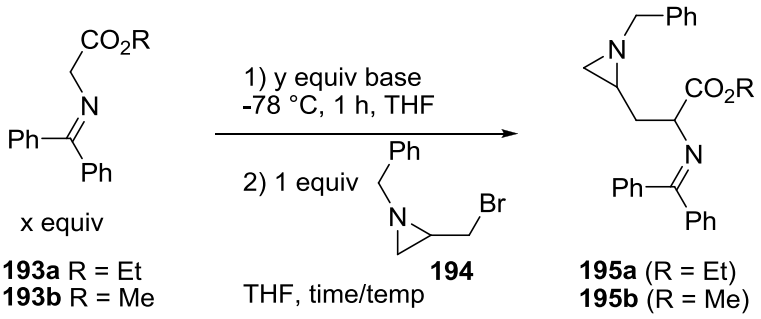
As has been pointed out within the literature overview, only one synthesis towards 2-(carboxyethyl)aziridines bearing an amino substituent at the α-position of the ester moiety has been reported to date. Therefore a first goal within this thesis was to develop new synthetic routes towards γ,δ-aziridino α-amino acid derivatives, *via* substitution of aziridines bearing a functionalized methyl substituent, suitable for nucleophilic substitution, at the 2-position with protected glycine derivatives. Having introduced the 2,4-diaminobutanoyl functionality these compounds now could serve as scaffolds for the synthesis of new DPP II inhibitors. Furthermore, ring transformation of these synthons to 2-(aminomethyl)-1-aminocyclopropanecarboxylic acid derivatives will give access to suitable building blocks for the synthesis of 2,3-methano analogues of Dab-Pip and for the synthesis of short model peptides to investigate their conformational behavior. Finally, within a last part of this thesis, the use of the *tert*-butanesulfinyl group will be investigated for the asymmetric synthesis of chiral 2-aryl-2-vinylaziridines. To that extent, the addition of different alkenylmagnesium bromides across aromatic α-halo *N*-(*tert*-butanesulfinyl)imines will be evaluated.

3.2 Synthesis and elaboration of γ,δ-aziridino α-amino acid derivatives

3.2.1 Synthesis of γ,δ-aziridino α-amino acid derivatives

1-Benzyl-2-(bromomethyl)aziridine **194** was chosen as starting material, a versatile substrate in organic synthesis with sufficient degree of reactivity towards nucleophiles due to the presence of the constrained azaheterocycle and the haloalkyl moiety.[20] Furthermore, this aziridine is easily prepared in high yield and purity *via* an optimized and frequently used procedure developed in our research group.[20b,20c,20k] The desired α,γ-diamino functionality was introduced by substitution of aziridine **194** with *N*-protected glycine esters **193a-b** and the synthesis of aziridino esters **195a-b** was carefully optimized by systematically changing the reaction conditions (Table 1).

Table 1. Synthesis of alkyl 3-(*N*-benzylaziridin-2-yl)-2-aminopropanoates 195a–b



Entry	Ester	Base	x equiv	y equiv	Time/Temp	Product	Conversion[a] (%)	dr[b]	Yield (%)[c]
1	**193a**	LiHMDS	1.1	1.1	1 h, -78 °C; 16 h, Δ	**195a**	0	-	-
2	**193a**	LiHMDS	1.5	1.5	1 h, -78 °C; 16 h, Δ	**195a**	10	1:1	-
3	**193a**	LiHMDS	2	2	16 h, r.t.	**195a**	0	-	-
4	**193a**	LiHMDS	2	2	16 h, Δ	**195a**	30	1:1	-
5	**193a**	LDA	2	2	16 h, Δ	**195a**	0	-	-
6	**193a**	LiHMDS	2	2	1 h, -78 °C; 16 h, Δ	**195a**	100	1:1	89
7	**193b**	LiHMDS	2	2	1 h, -78 °C; 16 h, Δ	**195b**	100	1:1	70
8	**193b**	LiHMDS	1	2	1 h, -78 °C; 16 h, Δ	**195b**	0	-	-

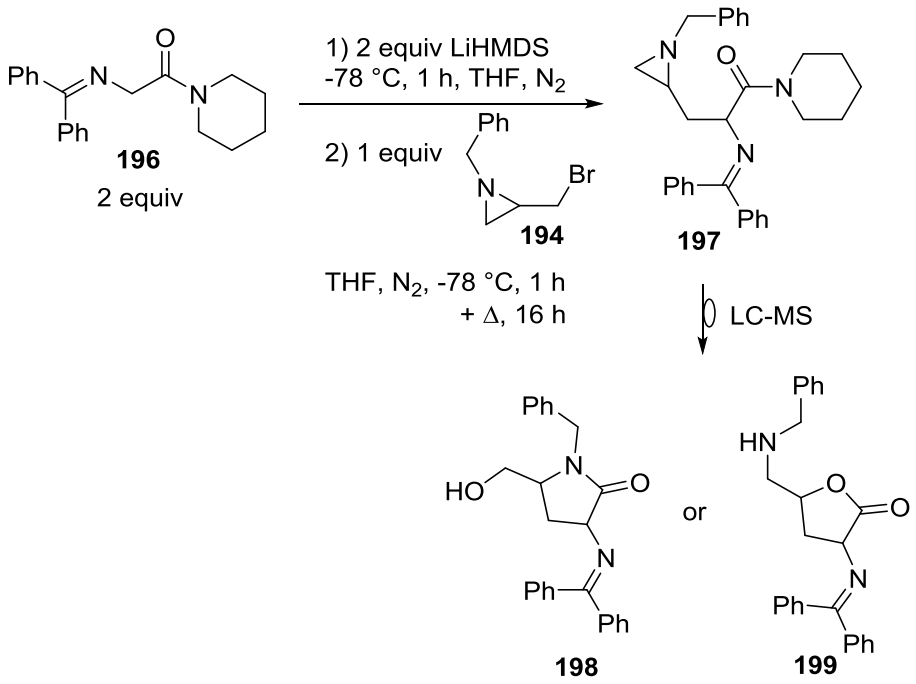
[a] Determined *via* ^{1}H NMR of the crude reaction mixture. [b] Determined *via* ^{1}H NMR after column chromatography. [c] Isolated yield after column chromatograpy

In a first attempt (entry 1), the substitution of compound **194** was performed with 1.1 equivalents of ethyl glycinate **193a**. After deprotonation of the ester **193a** with LiHMDS in THF at -78 °C, aziridine **194** was added and the mixture was stirred for one hour at -78 °C, followed by 16 hours at reflux in THF. After workup, the ^{1}H NMR of the crude reaction mixture indicated that no reaction had occurred. When the reaction was repeated with 1.5 equivalents of the enolate (entry 2), a conversion of only 10% was observed. The use of two equivalents of the enolate derived from glycine **193a**, reacting for 16 hours at room temperature (entry 3) also did not result in the formation of aziridino ester **195a**. When reflux was applied for two equivalents of the enolate (entry 4), a conversion of 30% was observed, and when LDA was used as an alternative base (entry 5) again no reaction occurred. Finally, the reaction was repeated with two equivalents of LiHMDS (entry 6) and the reaction mixture was stirred for one hour at -78 °C before heating under reflux for 16 hours. This time, the reaction was successful and the substitution product **195a** was isolated in 89% yield after purification by column chromatography. The same procedure was repeated with methyl glycinate **193b** (entry 7) and again the desired compound was isolated in 70% yield. Optimal conditions for the successful substitution of aziridine **194** thus include an additional hour of reaction time at -78 °C before heating under reflux for 16 hours after formation of the enolate derived from glycine esters

193 and addition of aziridine **194**. The need for the additional hour at -78 °C to get full conversion might be explained by the formation of a reactive complex between the enolate and aziridine **194** to avoid selfcondensation of the enolate, which occurs when reaction temperature is directly brought to reflux after addition of aziridine **194**. The substitution products **195a-b** were obtained as a 1:1 mixture of the $syn_{1,3}$ and $anti_{1,3}$ diastereomers, which could not be separated by column chromatography. In an additional attempt (entry 8), reaction of one equivalent of glycine ester **193b** with two equivalents of base resulted in degradation of the starting material.

3.2.2 Attempted synthesis of γ,δ-aziridino-α-amino amide derivatives

As the previously reported highly selective DPP II inhibitors all contain a 2,4-diaminobutanoylpiperidine skeleton (see chapter 1), it seemed interesting to perform the substitution reaction with glycine amide **196** as well, leading directly to substitution product **197** as a potential precursor of new conformationally constrained analogues of Dab-Pip **3** (Scheme 47). Similar reaction conditions as for the substitution reaction with *N*-(diphenylmethylene) glycine esters **193** were investigated. No reaction was observed after 30 minutes at -78 °C followed by 30 minutes at room temperature. However, after 16 hours of reflux, analysis of the crude reaction mixture (LC-MS, ^{1}H NMR) indicated the formation of a 1:1 mixture of two diastereomers. Comparison with the ^{1}H NMR spectrum of aziridine **195b** indeed implies the formation of the desired compound. Similar to the spectrum of aziridine **195b**, two AB-systems are observed in the range of δ = 3.0-3.6 ppm, which correspond to the chemical shifts of the benzylic CH_2 of both diastereomers. Furthermore, typical resonance signals in the range of δ = 4.1-4.5 ppm, corresponding to the CH at the α-position of the ester moiety of aziridine **195b**, were also observed in the crude spectrum of compound **197**. The mass spectroscopic data however did not match the expected mass of the desired compound **197** (LC-MS). A possible explanation for this observation might be a ring transformation into the corresponding lactam **198** or lactone **199**. As will be shown in section 3.2.3 and 3.2.4 of this thesis, these aziridines are highly susceptible towards ring transformation to the corresponding lactams and lactones. Unfortunately, all attempts to isolate the resulting diastereomers from the crude reaction mixture *via* column chromatography failed and only decomposition products were isolated.

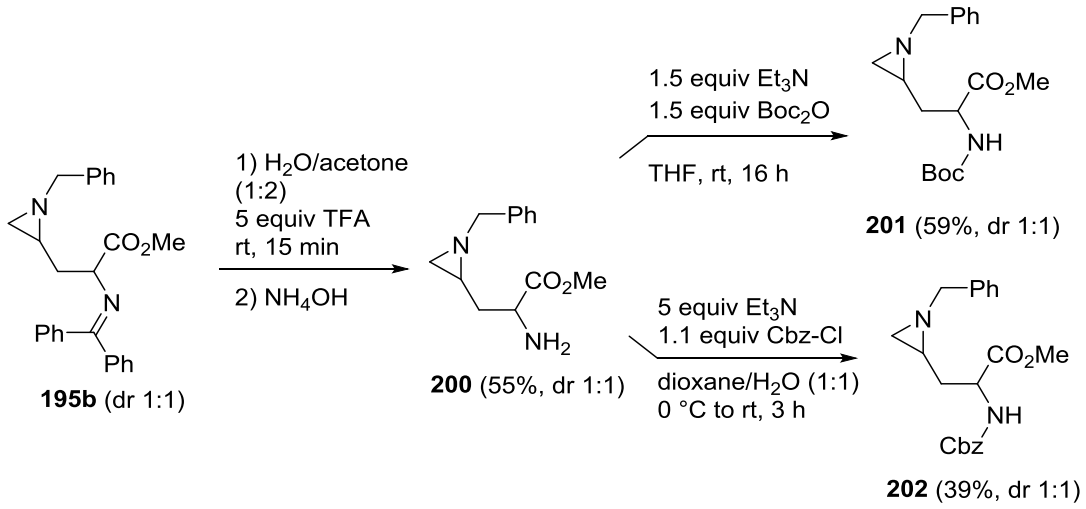


Scheme 47

3.2.3 Attempted saponification of γ,δ-aziridino α-amino acid derivatives

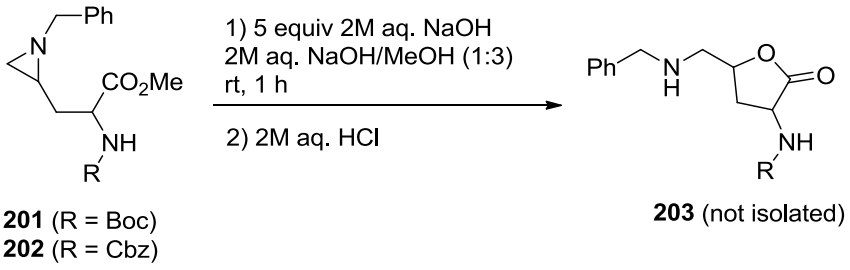
In order to synthesize the desired amide **197**, another route had to be developed, involving saponification of the ester function present in aziridines **195** followed by a coupling reaction with piperidine.

Attempts were made to do the saponification directly on the diphenylmethylidene protected aziridine **195b**. Unfortunately due to lack of stability of the imino function during acidic aqueous workup, saponification of this compound was not possible and other appropriate *N*-protecting groups had to be evaluated in order to allow this saponification. The *N*-diphenylmethylidene group of aziridine **195b** (Scheme 48) was cleaved by treatment of the aziridine with five equivalents of trifluoroacetic acid in a 2:1 mixture of acetone/water at room temperature for 15 minutes, resulting in the free amine **200** in 55% yield after basic workup with an aqueous NH_4OH solution. In a next experiment, the *tert*-butoxycarbonyl group was introduced as *N*-protecting group (Scheme 48) upon treatment of amine **200** with di-*tert*-butyl dicarbonate in the presence of triethylamine and compound **201** was isolated in 59% yield as a 1:1 mixture of diastereomers. The benzyloxycarbonyl protected amine **202** was also isolated in 39% yield (dr 1:1) upon reaction with Cbz-Cl in dioxane/water (1:1).



Scheme 48

Having the *N*-Boc and *N*-Cbz protected aziridines **201** and **202** in hand, attempts were made to hydrolyse the ester function under basic conditions (Scheme 49). Aziridines **201** and **202** were treated with five equivalents of 2M aq. NaOH in a 1:3 mixture of 2M NaOH/MeOH. The progress of the reaction was followed by thin layer chromatography and after one hour of stirring at room temperature all starting material was consumed. Methanol was evaporated and the residue was acidified with aq. 2M HCl before extraction with an organic solvent. Hydrolysis of 2-(cyanoethyl)aziridines under basic conditions (see section 2.6) showed that the resulting potassium carboxylates were isolated but a ring expansion to the corresponding lactones occurred upon treatment of these salts with acetic acid. These findings, together with the ^{1}H NMR and LC-MS analysis of the reaction mixture, suggest indeed the formation of lactones **203**. Unfortunately, all attempts to isolate these compounds **203** *via* column chromatography failed.

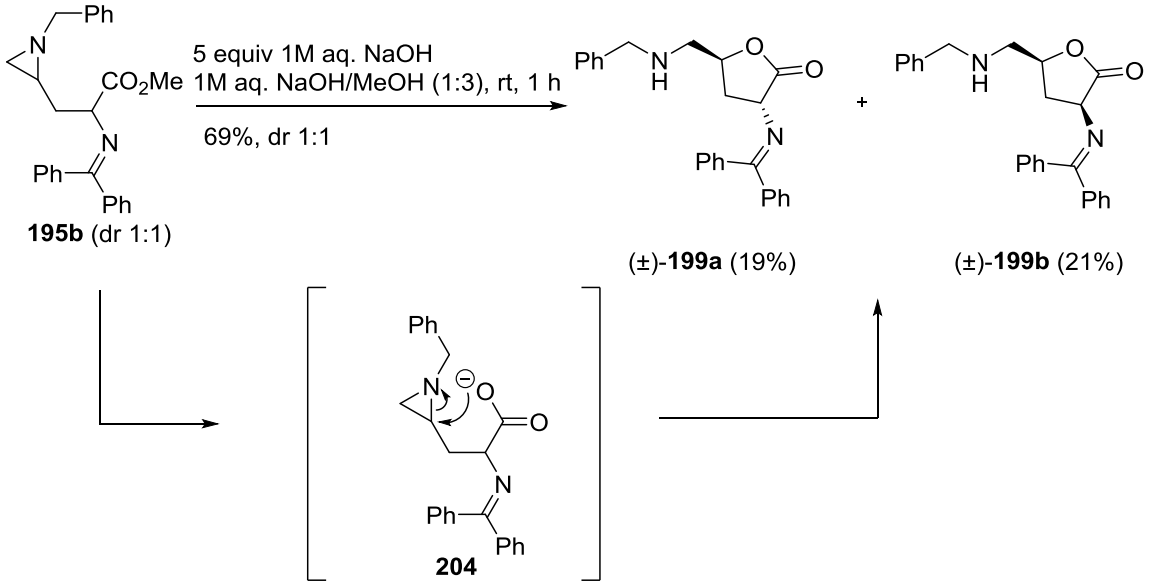


Scheme 49

Since a ring transformation to the corresponding γ-butyrolactones **203** seems unavoidable upon acidic workup, the possibility was investigated to isolate the sodium salts instead. The same reaction conditions were applied as before but this time the aqueous residue was not treated with HCl before extraction. Comparison of LC-MS results with the previously obtained ones indicated that the lactone

had already been formed under basic conditions. Again it was impossible to obtain the pure compound after column chromatography.

The same reaction conditions were applied to *N*-diphenylmethylidene-protected aziridine **195b** to verify if also in this case ring expansion of carboxylate **204** to the corresponding lactone occurred under basic conditions and if so, if the pure compounds could be isolated. Indeed a 1:1 mixture of γ-lactones **199** was obtained and both diastereomers were isolated in 69% combined yield (Scheme 50). Formation of the corresponding δ-lactone was not observed, probably due to a disfavored 6-*endo-tet* ring closure according to Baldwin's rules as compared to a favored 5-*exo-tet* cyclization. Finally, both diastereomers were separated from each other to yield (±)-**199a** and (±)-**199b** in 19% and 21% yield, respectively, using preparative TLC.



Scheme 50

Formation of γ-lactam **198** can also be excluded, based upon comparison with experimental data for similar γ-lactones from literature[20a] and γ-lactams **205**, (±)-**215** and (±)-**211a**, the synthesis of which is described within the next section (see section 3.2.4, experimental section). A first indication is the difference in value of the C=O stretching vibration, equal to 1771 and 1772 for isomer (±)-**199a** and (±)-**199b**, respectively, in the IR-spectra. While similar γ-lactones show a typical value of about 1770 cm^{-1}, all synthesized γ-lactams show a value around 1680-1690 cm^{-1}. A second indication is the ^{1}H NMR-chemical shift of the benzylic CH_2. For all synthesized lactams, both protons show an AX-system which resonates downfield at δ = 4.0-4.2 ppm and δ = 4.9-5.1 ppm with a difference in δ-value of about 1 ppm. For both isomers (±)-**199a** and (±)-**199b** however, an AB-system which resonates around 3.7-3.9 ppm with a smaller difference in δ-value (0.04 ppm) is visible, which is in accordance

with data from similar γ-lactones. Finally, a difference in chemical shift is observed for H_a (Figure 7 and 9) of the resulting lactones and lactams, respectively. The proton H_a resonates between δ = 3.5-4.0 ppm for all synthesized lactams, while H_a of isomers (±)-**199a** and (±)-**199b** resonates at δ = 4.5-5.0 ppm.

The relative stereochemistry of both diastereomers was assigned *via* a combined analysis of observed coupling constants and 1D-NOESY experiments (Figure 7). Only in the case of isomer (±)-**199a**, both methylene protons H_b and H_c are resolved in the ^{1}H NMR spectrum and therefore only coupling constants of this isomer can be compared. H_a (multiplet) and H_d (dxd) can be unambiguously assigned from the ^{1}H NMR spectrum based on their multiplicity. H_d (dxd, 4.43 ppm) of isomer (±)-**199a** exhibits two vicinal coupling constants, J_{cd} = 8.2 Hz and J_{bd} = 5.7 Hz. The assignment of H_b and H_c was made, assuming that a *cis*-relationship would give the largest coupling constant. The signal of H_c (dxdxd, 2.18 ppm) shows a geminal coupling constant of J_{bc} = 13.0 Hz and two vicinal ones, being J_{cd} = 8.2 Hz and J_{ac} = 5.5 Hz, which confirms the *cis*-relationship of H_c and H_d and suggests a *trans*-coupling between H_c and H_a. H_b (dxdxd, 2.50 ppm) again exhibits a geminal coupling constant of J_{bc} = 13.0 Hz and two vicinal ones of J_{ab} = 7.6 Hz and J_{bd} = 5.7 Hz, which now confirms the *trans*-relationship of H_b and H_d and *cis*-relationship of H_b and H_a. Based on these findings it can be concluded that the two substituents of isomer (±)-**199a** should be *trans* opposed to each other.

However, no firm assignments of stereochemistry can be made based on the size of coupling constants alone, and therefore 1D transient NOESY experiments were performed on both diastereomers (Figure 7, experimental section). The traditional steady-state 1D NOE experiment involves saturation at the resonance frequency of one peak in the ^{1}H NMR spectrum with low power radio frequency. Then a 90° pulse is applied and an FID is recorded to measure the amount of perturbation on the nearby nuclei. Since the enhancement of signals is quite small, it is necessary to record a control spectrum and to subtract the control spectrum from the NOE spectrum (NOE difference). With shaped (selective) pulses a 180° pulse can be applied specifically to a single peak in the spectrum. After a short time this perturbation propagates to nearby nuclei and a 90° pulse will "read" the effect on the other nuclei in the form of a spectrum with enhanced peak areas. In principle, a NOE spectrum similar to a NOE difference spectrum is obtained but the transient NOE does not involve the subtraction of spectra and therefore practically no artifacts are observed.[65]

When H_a of isomer (±)-**199a** was irradiated, a negligible increase in the signal of H_d (0.3%) was observed while a substantial NOE of 5.6% for H_b (2.50 ppm) and a very small NOE of 0.3% for H_c (2.18 ppm) was observed. These results now indeed suggest a *trans*-relationship of H_a and H_d in isomer (±)-**199a** and indicate a *cis*-relationship between H_a and H_b and thus confirm the hypothesis made

based upon the size of the coupling constants. To unambiguously prove the *trans*-relationship of both substituents in lactone (±)-**199a**, H_a of isomer (±)-**199b** was also irradiated. In this case, a significant increase in the signal of H_d of 3.2% was observed. Furthermore, a substantial NOE of 5.2% for the signal of H_b and H_c (m, 2.37-2.44 ppm) was observed. Since both protons are not resolved in the ^{1}H NMR spectrum no further conclusions about the relative position of H_b and H_c towards H_a can be drawn. From these results, in can be concluded that the relative stereochemistry of lactones (±)-**199a** and (±)-**199b** can be assigned as (±)-*trans*-**199a** and (±)-*cis*-**199b**.

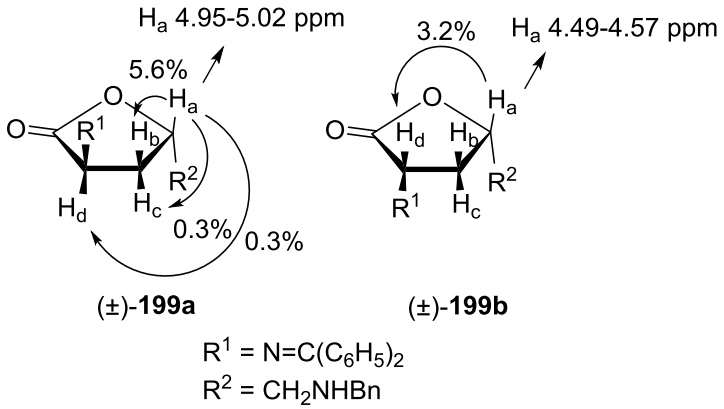
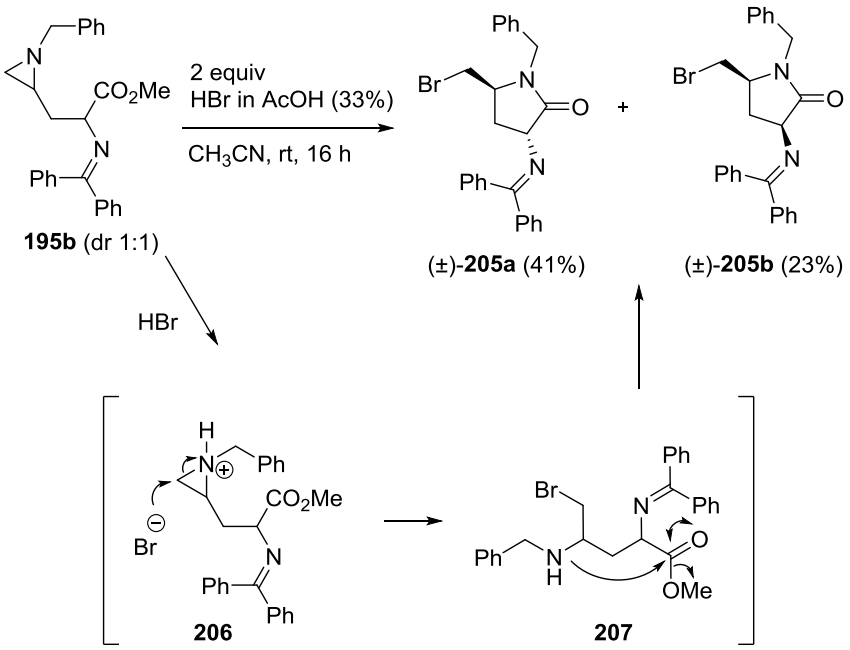


Figure 7. Determination of the *trans*- and *cis*-stereochemistry of lactones (±)-199

3.2.4 Ring transformation of γ,δ-aziridino-α-amino acid derivatives into 5-(bromomethyl)pyrrolidinones

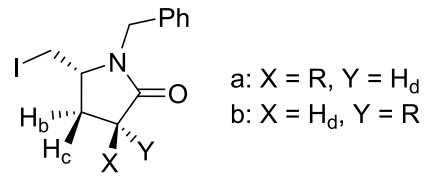
Having the desired conformationally constrained γ,δ-aziridino α-amino ester **195b** in hand, its application as synthetic building block was investigated. Treatment of aziridine **195b** with 2 equivalents of a 33% HBr solution in glacial acetic acid resulted in the formation of a 1:1 diastereomeric mixture of 5-(bromomethyl)pyrrolidinones **205** (Scheme 51). This time, regioselective ring opening occurred at the unsubstituted aziridine carbon atom of the intermediate aziridinium salt **206**, which is in accordance with previously observed results concerning the ring opening of 2-(cyanomethyl)aziridines with HBr.[66] Intramolecular ring closure of the resulting α,γ-diamino ester **207** resulted in the formation of pyrrolidinones **205**.



Scheme 51

One of the diastereomers spontaneously precipitated from the crude reaction mixture upon addition of Et_2O and was easily isolated in 41% yield, while column chromatography afforded the other isomer as a pure compound in 23% yield.

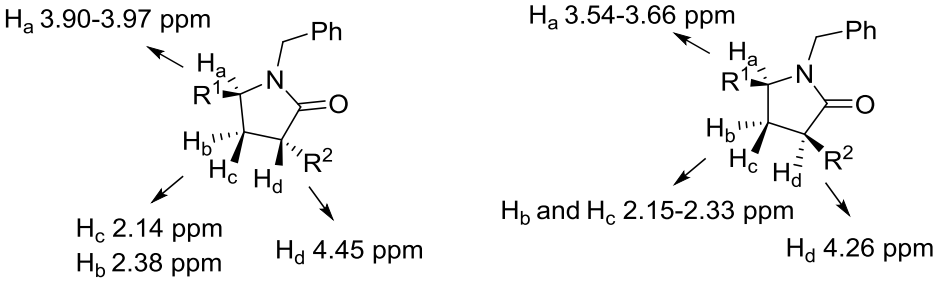
To assign the relative *cis*/*trans* stereochemistry of both diastereomers, ^{1}H NMR spectroscopic data of both diastereomers was compared with literature data for similar substituted pyrrolidinones. Momose and co-workers reported the synthesis of related 3,5-disubstituted pyrrolidin-2-ones (±)-**208**-(±)-**213** by iodolactamization *via* homoallylic asymmetric induction (Figure 8).[67] Assignment of the *trans*- or *cis*-relationship between the C-3 substituent and the iodomethyl group was achieved by the characteristic ^{1}H NMR chemical shift data of the methylene protons H_b and H_c at C-4 (Figure 8). In the case of the *cis*-isomers, the signals for H_b and H_c are split into two sets of signals, usually separated by 0.5-1.1 ppm, while for the *trans*-isomers the methylene signals usually overlap or the difference in chemical shift is smaller. Furthermore, the *trans*-relationship of the substituents in pyrrolidinone (±)-**211a** was confirmed by X-ray diffraction analysis.



(±)-**208a,b** (R = Me)
(±)-**209a,b** (R = Ph)
(±)-**210a,b** (R = cyclohexyl)
(±)-**211a,b** (R = CbzNH)
(±)-**212a,b** (R = BocNH)
(±)-**213a,b** (R = BnO)

Figure 8. Lactams synthesized by Momose and co-workers[67]

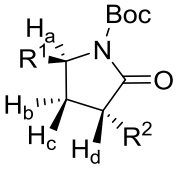
Comparison of these findings with the experimental data of the synthesized pyrrolidinones (±)-**205a** and (±)-**205b** (Figure 9), could suggest a *cis*-relationship of the bromomethyl and diphenylmethylideneamino substituents of compound (±)-**205a**. The methylene signals of isomer (±)-**205a** are clearly split into two resolved signals while those for isomer (±)-**205b** overlap to form a multiplet.



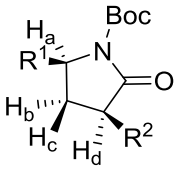
(±)-**205a** $R^1 = CH_2Br$ $R^2 = N{=}C(C_6H_5)_2$ (±)-**205b**

Figure 9. Spectroscopic data of γ-lactams (±)-205

A more detailed look into literature showed the same pattern in a series of *N*-Boc-protected 3,5-disubstituted pyrrolidin-2-ones **214** (Figure 10). Furthermore, it was observed that H_a signals are deshielded in the *trans*-isomers in comparison with the corresponding *cis*-isomers and for all *trans* compounds, the coupling constants J_{ab} and J_{ac} are very different from each other while those for the *cis*-isomers are similar.[68]



(±)-**214a**



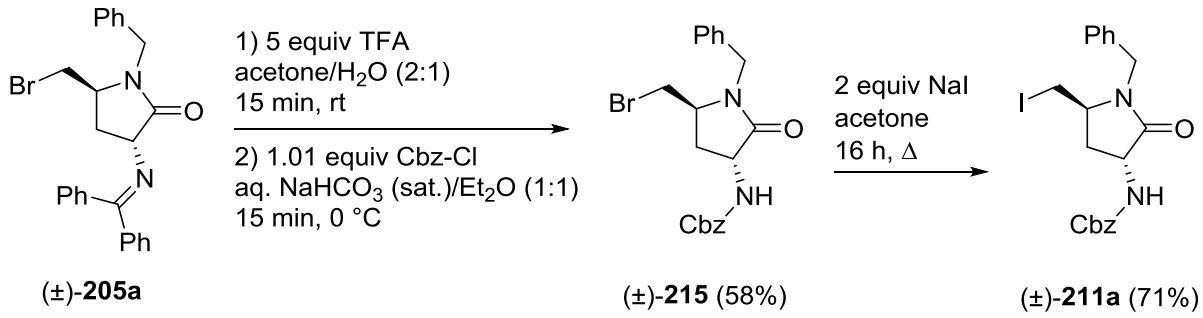
(±)-**214b**

R^1 = CO_2Et, CO_2t-Bu, Me, Ph
R^2 = CH_2CO_2Et, CH_2CN, allyl, $CH_2CH{=}CHC_6H_5$, Bn, Me

Figure 10. *N*-Boc-protected 3,5-disubstituted pyrrolidin-2-ones[68]

These additional findings now suggested a *trans*-relationship in compound (±)-**205a**. Indeed, H_a of isomer (±)-**205b** (m, 3.54-3.66 ppm) resonates at a lower delta value of as compared to H_a of isomer (±)-**205a** (m, 3.90-3.97 ppm). In the case of isomer (±)-**205a**, H_d (dxd, 4.45 ppm) exhibits two vicinal coupling constants, J_{cd} = 8.3 Hz and J_{bd} = 6.1 Hz. H_a (multiplet) and H_d (dxd) can be unambiguously assigned from the ^{1}H NMR spectrum based on their multiplicity, the assignment of H_b and H_c was made, assuming that a *cis*-relationship would give the largest coupling constant. The signal of H_c (dxdxd, 2.14 ppm) shows a geminal coupling constant of J_{bc} = 13.2 Hz and two vicinal ones, being J_{cd} = 8.3 Hz and J_{ac} = 3.9 Hz, which confirms the *cis*-relationship of H_c and H_d and suggests a *trans*-coupling between H_c and H_a. H_b (dxdxd, 2.38 ppm) again exhibits a geminal coupling constant of J_{bc} = 13.2 Hz and two vicinal ones of J_{ab} = 8.3 Hz and J_{bd} = 6.1 Hz, which now confirms the *trans*-relationship of H_b and H_d and *cis*-relationship of H_b and H_a. Based on these findings, which should be interpreted with some precaution, it can be concluded that the two substituents of isomer (±)-**205a** should be *trans* opposed to each other.

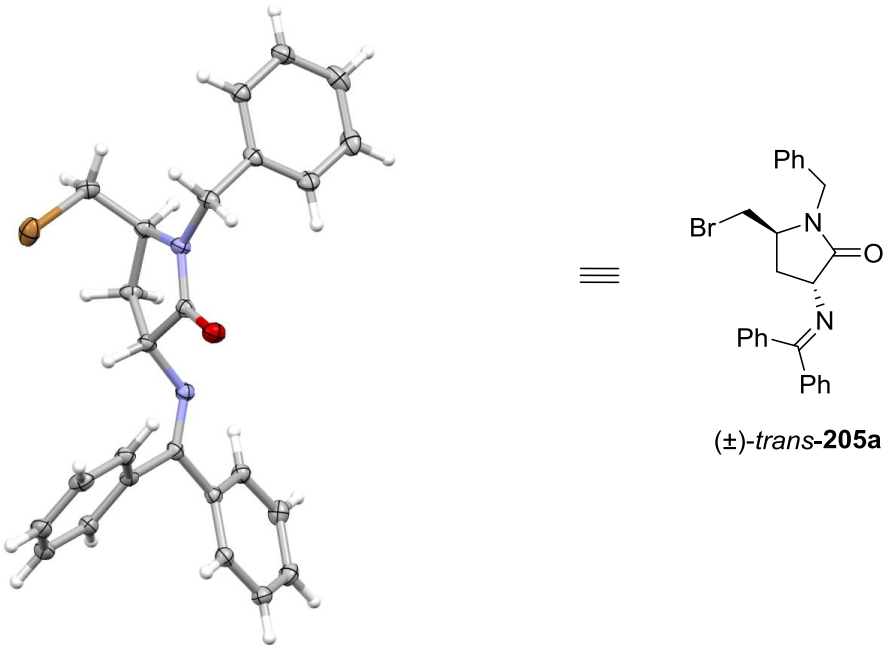
Interestingly, isomer (±)-**205a** was easily transformed into the known compound (±)-**211a** for comparison of its spectroscopic data (Scheme 52).[67] Deprotection using 5 equivalents of TFA in a 2:1 mixture of acetone/water gave the free amine, which was used without further purification in the next step. Reaction with benzyl chloroformate afforded Cbz-protected pyrrolidinone (±)-**215** in 58% overall yield. Exchange of halogen atoms *via* Finkelstein reaction subsequently afforded 5-(iodomethyl)pyrrolidinone (±)-**211a** in 71% yield. Comparison of ^{1}H NMR spectra with literature data for (±)-*trans*-**211a**,[67] showed both compounds to be identical, thus supporting the *trans*-substitution in pyrrolidinone(±)-**205a**.



(±)-**205a** (±)-**215** (58%) (±)-**211a** (71%)

Scheme 52

The stereochemistry of isomer (±)-**205a** was finally unambiguously assigned as (±)-*trans*-**205a** by X-ray diffraction analysis (in collaboration with Prof. K. Van Hecke, Inorganic and Physical Chemistry, Ghent University, Belgium) (Figure 11).



(±)-*trans*-**205a**

Figure 11. X-ray diffraction analysis of *trans*-pyrrolidinone (±)-*trans*-205a

3.2.5 Stereoselective ring transformation of γ,δ-aziridino-α-amino acid derivatives into 2-(aminomethyl)-1-aminocyclopropanecarboxylic acid derivatives

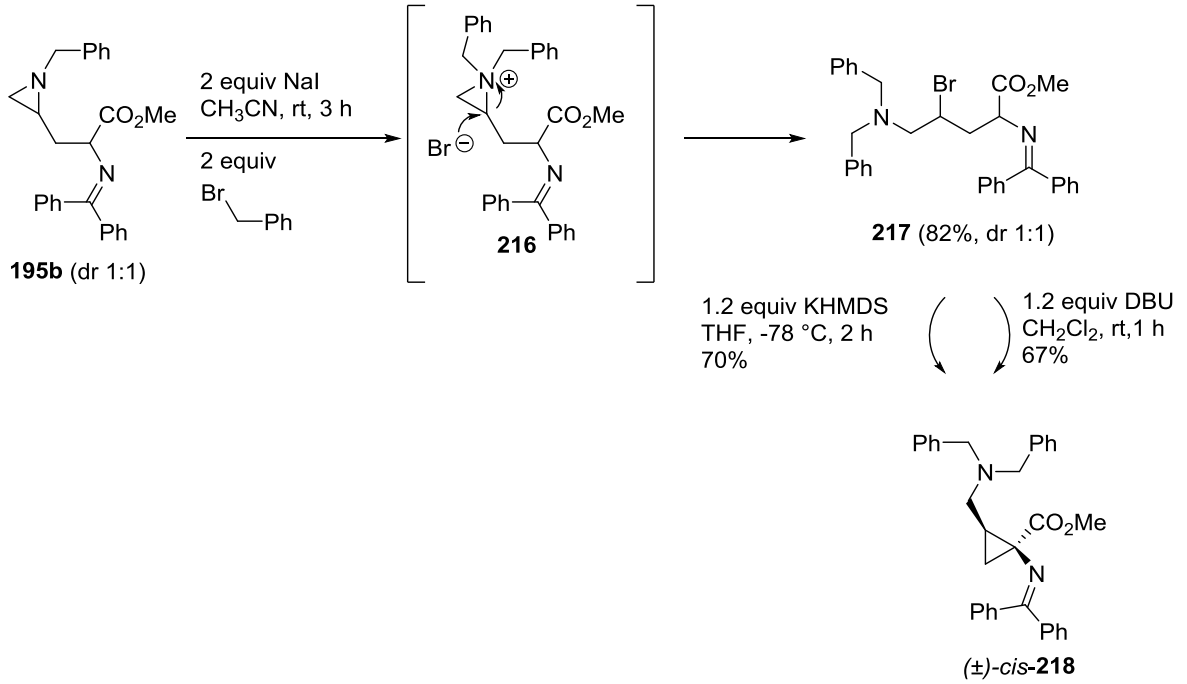
The first synthesis of the naturally-occurring 2-aminomethyl-substituted ACC derivative carnosadine **11**, involved a cyclopropanation of a functionalized α,β-dehydroamino acid, followed by a resolution step which allowed assignment of the absolute configuration.[16] A key step towards the first asymmetric synthesis of carnosadine was the synthesis of chiral 2-hydroxymethyl-ACC (2,3-methanohomoserine) *via* double alkylation of a chiral aminonitrile synthon with epibromohydrin after which the primary hydroxyl group can easily be transformed into a variety of other functional groups.[69] All known syntheses towards 2-aminomethyl-substituted ACC derivatives proceed *via* this

key intermediate. Entries towards this intermediate involve double alkylation of a chiral glycine equivalent with enantiopure epichlorohydrins as bifunctional electrophiles,[70] or diastereoselective cyclopropanation of a homochiral dehydroamino acid derivative, obtained from D-mannitol.[71] Finally, the asymmetric synthesis of all stereoisomers of carnosadine was performed *via* reaction of cyclic sulfates with malonate diesters.[72]

Aziridines have already demonstrated their utility as valuable substrates for ring transformation to cyclopropanes.[21] In order to prepare a ring transformation towards 2-(aminomethyl)-cyclopropanecarboxylic acid derivatives, thus avoiding the intermediacy of 2-hydroxymethyl-ACC derivatives, the introduction of a potential leaving group in γ-position of the α-amino ester moiety *via* ring opening of aziridine **195b** was investigated.

As previously reported for the ring opening of related aziridines,[21a] aziridine **195b** was treated with benzyl bromide in acetonitrile under reflux which resulted in degradation of the starting material however. The reaction was repeated at room temperature but this time no reaction occurred and starting material was recovered. Finally, treatment of aziridine **195b** with benzyl bromide at room temperature in acetonitrile in the presence of two equivalents of NaI afforded β-bromo amine **217** as a single regioisomeric product in 82% yield in a 1:1 diastereomeric ratio (Scheme 53). Benzyl bromide is responsible for both the activation of the aziridine ring leading to the aziridinium salt **216** and for the delivery of the nucleophilic bromide anion which induces ring opening of the aziridinium ion at the more-hindered aziridine carbon atom, which is in accordance with previously observed reactivity of related aziridines.[73] Formation of the β-iodo amine was not observed and previous research has shown that substitution of bromine for iodine in the ring opening product of related aziridines proceeds *via* the aziridinium salt intermediate.[74] To complete this substitution, three hours at reflux and 20 equivalents of NaI were necessary. When 15 equivalents were used, a longer reaction time of five hours was required. This clearly indicates the lower reactivity of the iodide ion and thus explains why no formation of the iodo derivative is observed under the conditions used here.

Deprotonation at the α-position of the ester moiety, assisted by the iminated α-amino function,[75] and bromide expulsion through intramolecular nucleophilic displacement gave a ring closure toward cyclopropane (±)-*cis*-**218** with excellent diastereoselectivity (dr 98:2). Both KHMDS and DBU were used as a base for this cyclopropane formation, and in each case the cyclopropane (±)-*cis*-**218** was isolated, after column chromatography followed by recrystallization from ethanol, as a single diastereomer (dr > 99:1) in 67-70% yield (Scheme 53). The stereochemistry was unambiguously assigned as *cis*-cyclopropane (±)-*cis*-**218** by X-ray diffraction analysis (in collaboration with Prof. K. Törnroos, Department of Chemistry, University of Bergen, Norway) (Figure 12).[76]



Scheme 53

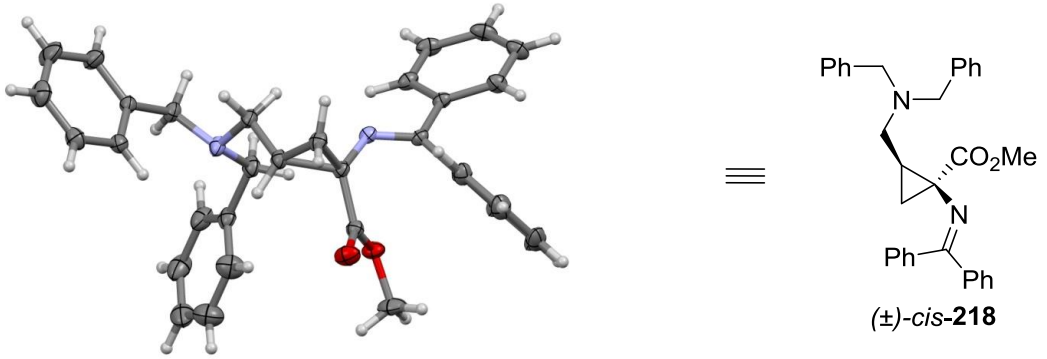


Figure 12. X-ray diffraction analysis of *cis*-cyclopropane (±)-*cis*-218

The *cis*-stereoselectivity obtained in the cyclization of the isomeric mixture of γ-bromo-α,δ-diamino esters **217** can be rationalized by steric effects and implicates a preferred conformation as present in the proposed transition state TS-A (Figure 13).[77] Transition state TS-B, leading to the *trans*-cyclopropane is disfavored due to steric interactions between the dibenzylaminomethyl moiety and the 'enolate' group, which appear to be greater than those between the dibenzylaminomethyl moiety and the 'diphenylmethylidenamino' group. In contrast to the smaller ester group of the final cyclopropanes **218**, the effective steric bulk of the 'enolate' group (involving the counterion M^+) is larger than that of the 'diphenylmethylidenamino' group. Furthermore, TS-A might be stabilized *via*

π-π interactions between the aromatic rings. The observed *cis*-stereoselectivity is in accordance with previously reported results concerning the ring closure of similar substrates.[78]

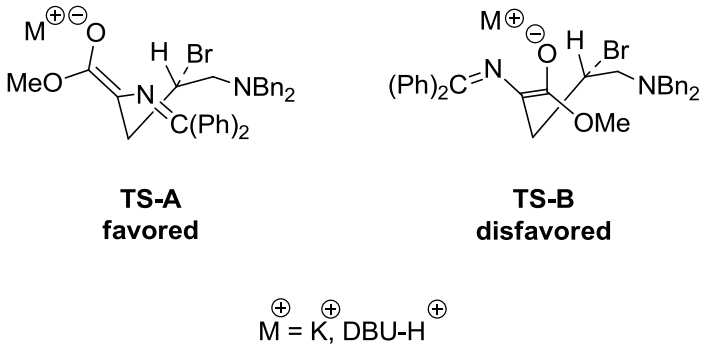
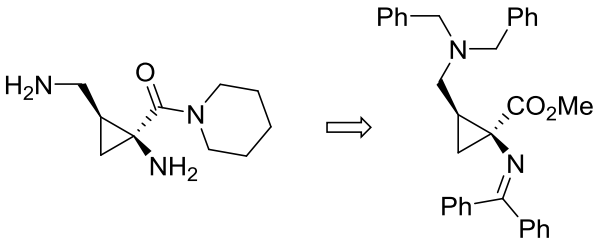


Figure 13. Proposed transition-state model for the synthesis of *cis*-cyclopropane (±)-*cis*-218

In conclusion, new conformationally constrained α,γ-diamino acid derivatives **195a-b** were synthesized *via* substitution of 1-benzyl-2-(bromomethyl)aziridine **194** with different protected glycine esters **193**. Substitution with protected glycine amide **196** to synthesize the conformationally constrained analogue **197** of Dab-Pip **3** failed however and other synthetic routes towards this compound should be investigated. The use of methyl 3-(aziridin-2-yl)-2-aminopropanoate **195b** as building block for other organic molecules was subsequently investigated. Saponification of the latter compound resulted in the formation of a diastereomeric mixture of γ-lactones **199**. Both isomers were separated *via* column chromatography and the relative stereochemistry of both diastereomers was assigned using NOE-experiments. Treatment of aziridine **195b** with HBr led to a 1:1 diastereomeric separable mixture of γ-lactams **205**, whose relative stereochemistry was unambiguously assigned *via* X-ray diffraction analysis. Finally, aziridine **195b** proved to be an excellent substrate for ring transformation into the corresponding stereochemically defined *cis*-2-(aminomethyl)-1-aminocyclopropanecarboxylic acid derivative (±)-*cis*-**218**, the structure of which was also confirmed by X-ray diffraction analysis.

3.3 Synthesis of 2,3-methano analogues of (*S*)-2,4-diaminobutanoylpiperidine Dab-Pip

The previously synthesized 2-aminomethyl-substituted 1-aminocyclopropane-1-carboxylic acid (ACC) derivative (±)-*cis*-**218** now could serve as building block for the 2,3-methano analogue (±)-**219** of Dab-Pip **3** as a potential conformationally constrained inhibitor of dipeptidyl peptidases (Scheme 54).[79]

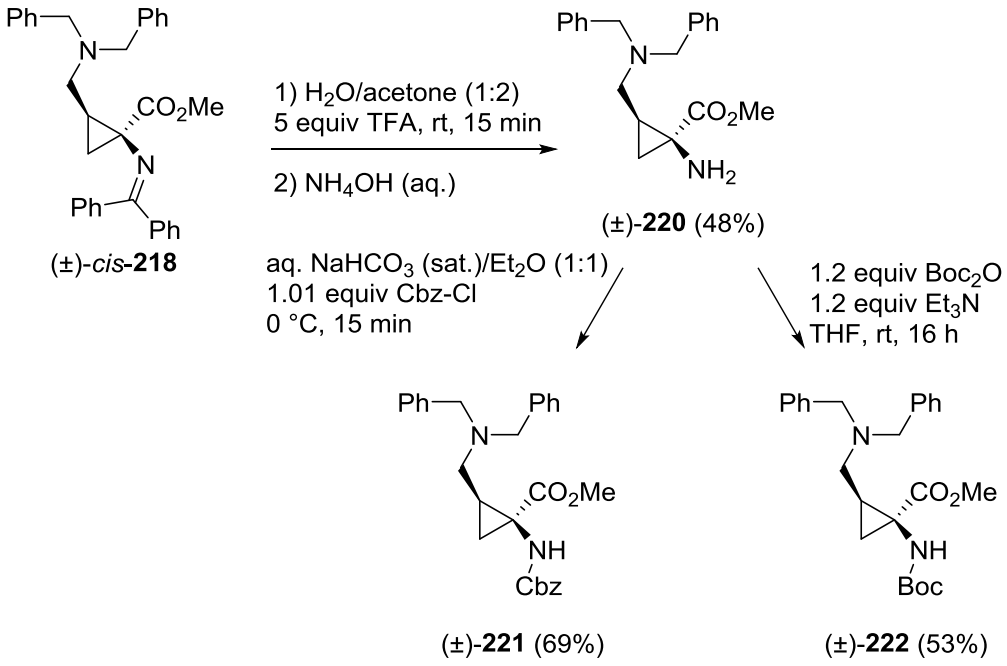


(±)-**219** (±)-*cis*-**218**

Scheme 54

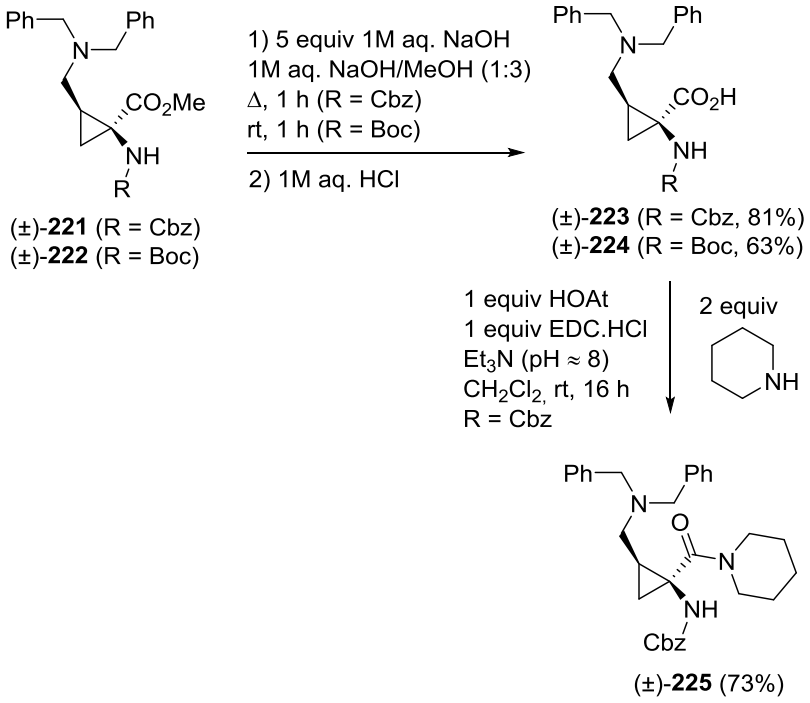
A route was developed to introduce the amide functionality, involving saponification of the ester function present in cyclopropane (±)-*cis*-**218** followed by a coupling reaction with piperidine. This transformation proved to be difficult. Attempts were made to perform the saponification directly on the *N*-diphenylmethylidene-protected cyclopropane (±)-*cis*-**218**, but unfortunately, due to lack of stability of the imino function during aqueous workup, a selective saponification of this compound was not possible and again other appropriate *N*-protecting groups had to be introduced in order to achieve this saponification.

The *N*-diphenylmethylidene group of cyclopropane (±)-*cis*-**218** was hydrolysed by treatment with five equivalents of trifluoroacetic acid in a 2:1 mixture of acetone/water at room temperature for 15 minutes, resulting in the free amine (±)-**220** in 48% yield after basic workup with aqueous NH_4OH (Scheme 55). Subsequently, the benzyloxycarbonyl group was introduced as *N*-protecting group upon treatment of amine (±)-**220** with 1.01 equivalents of Cbz-Cl in saturated aqueous $NaHCO_3/Et_2O$ (1:1) providing *N*-Cbz protected α-aminocyclopropanecarboxylic ester (±)-**221** in 69% yield. Reaction of amine (±)-**220** with 1.2 equivalents of Boc_2O resulted in the formation of *N*-Boc protected cyclopropanecarboxylic ester (±)-**222** in 53% yield.



Scheme 55

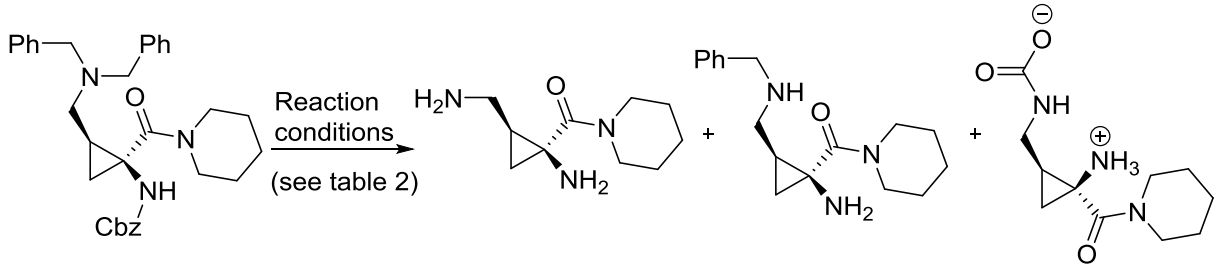
Saponification with 1M aqueous NaOH/MeOH (1:3), followed by acidic workup with aqueous HCl afforded carboxylic acids (±)-**223** and (±)-**224** in 81% and 63% yield respectively (Scheme 56). Subsequent reaction of cyclopropanecarboxylic acid (±)-**223** with piperidine at room temperature for 16 hours in the presence of EDC.HCl as coupling reagent led to amide (±)-**225** in 73% yield.



Scheme 56

Complete deprotection of the latter compound would then lead to the desired 2,3-methano-analogue (±)-**219** of (*S*)-2,4-diaminobutanoylpiperidine **3** (Table 2). In a first experiment, deprotection was tried with palladium on carbon (20%) in methanol under reflux in the presence of five equivalents of ammonium formate as hydrogen source, resulting in complete deprotection of cyclopropane (±)-**225** (Entry 1). Upon standing however, a white precipitate was formed within the reaction mixture. A possible explanation for this observation could be the reaction of completely deprotected cyclopropane (±)-**219** with carbon dioxide, resulting in the formation of ammonium carbamate (±)-**227**, which is in accordance with the observed mass in LC-MS. Indeed, aliphatic amines are known to react promptly with CO_2 to afford the corresponding ammonium carbamate.[80] The use of palladium hydroxide on carbon in methanol under H_2 atmosphere (5 bar) resulted in a mixture of the completely deprotected cyclopropane (±)-**219** and the monodebenzylated cyclopropane (±)-**226** after 20 hours at room temperature (Entry 2). The catalyst was switched to palladium on carbon but after reacting for four hours under H_2 atmosphere of 5 bar, decomposition of the starting material was observed, resulting in a complex reaction mixture (Entry 3). In a next experiment a milder pressure of 2 bar was applied which resulted in the formation of a mixture of completely deprotected and monodebenzylated cyclopropanes (±)-**219** and (±)-**226** after 30 minutes or two hours of reaction time (Entry 4-5). Finally, after four hours, reaction was complete and the deprotected cyclopropane (±)-**219** was isolated in 91% yield (Entry 6).

Table 2. Deprotection of cyclopropane (±)-225



(±)-**225** (±)-**219** (±)-**226** (±)-**227**

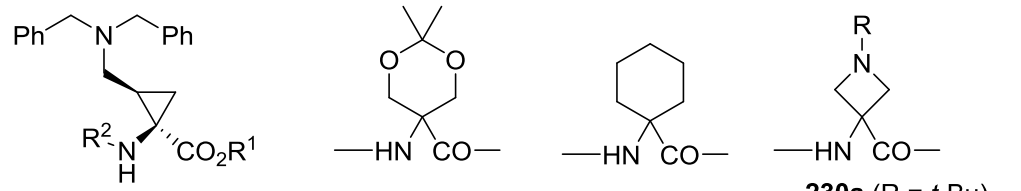
Entry	Reaction conditions	Result
1	5 equiv NH_4HCO_2, 20% Pd/C MeOH, Δ, 30 min	Complete deprotection Mixture of (±)-**219** and (±)-**227**
2	20% $Pd(OH)_2$/C, H_2 (5 bar), MeOH, rt, 20 h	Mixture of (±)-**219** and (±)-**226**
3	20% Pd/C, H_2 (5 bar), MeOH, rt, 4 h	Complex reaction mixture
4	20% Pd/C, H_2 (2 bar), MeOH, rt, 30 min	Mixture of (±)-**219** and (±)-**226**
5	20% Pd/C, H_2 (1.8 bar), MeOH, rt, 2 h	Mixture of (±)-**219** and (±)-**226**
6	20% Pd/C, H_2 (1.8 bar), MeOH, rt, 4 h	Complete deprotection (±)-**219**, 91%

In conclusion, cyclopropane (±)-*cis*-**218** could serve as building block for the synthesis of 2,3-methano analogue (±)-**219** of Dab-Pip **3**. Coupling with piperidine and subsequent deprotection of the amino functions led to the new conformationally constrained 2,4-diaminobutanoylpiperidine derivative (±)-**219**. An asymmetric synthesis of these 2-aminomethyl-ACC derivatives and the corresponding *N*-(α,γ-diaminoacyl)pyrrolidine and -piperidine derivatives from cyclopropanecarboxylic acids (±)-**223** and (±)-**224** should be prepared in future research. Biological evaluation of these molecules will help fill the gaps in the knowledge of SAR of dibasic inhibitors of DPP II and other catalytically active dipeptidyl peptidases such as DPP IV, DPP8 and DPP9. Furthermore, for the latter targets, several structurally related dibasic compounds have been reported as highly potent inhibitors.[81]

3.4 Synthesis of model peptides containing 2-(aminomethyl)-1-aminocyclopropanecarboxylic acid derivatives

In a next part, the previously synthesized conformationally constrained C^{α}-tetrasubstituted α,γ-diamino acid residues R^2-$AMAc_3c$-OR^1 (±)-**220**, (±)-**223** and (±)-**224** were used to carry out the synthesis of selected model peptides to study the conformational bias they impart to a peptide chain. The use of C^{α}-tetrasubstituted α-amino acids to restrict backbone conformations of peptides

and to inhibit biodegradation has already been demonstrated,[82] making these amino acids interesting building blocks for the design of peptidomimetic drugs. The conformational preferences of peptides containing a cycloaliphatic residue Ac_nc (n = 3–8) have already been investigated thoroughly,[83] but the influence of an extra substituent on this cycloaliphatic moiety has not been fully studied so far. Furthermore, previous research has shown that the oxygen atoms of the 1,3-dioxane system of residue **228** may act as H-bond acceptors for amide NHs (Figure 14).[84] These main-chain to side-chain intramolecular H-bonds destabilize the 3_{10}-helical structures, typically adopted by the related homopeptides containing the Ac_6c residue **229**. Similarly, the nitrogen present in the azetidine ring of residue **230** also forms a main-chain to side-chain intramolecular H-bond when incorporated into small peptides.[85]



(±)-**220** (R^1 = Me, R^2 = H)
(±)-**223** (R^1 = H, R^2 = Cbz)
(±)-**224** (R^1 = H, R^2 = Boc)
R^2-$AMAc_3c$-OR^1

228 **229**

230a (R = *t*-Bu)
230b (R = *t*-Amyl)

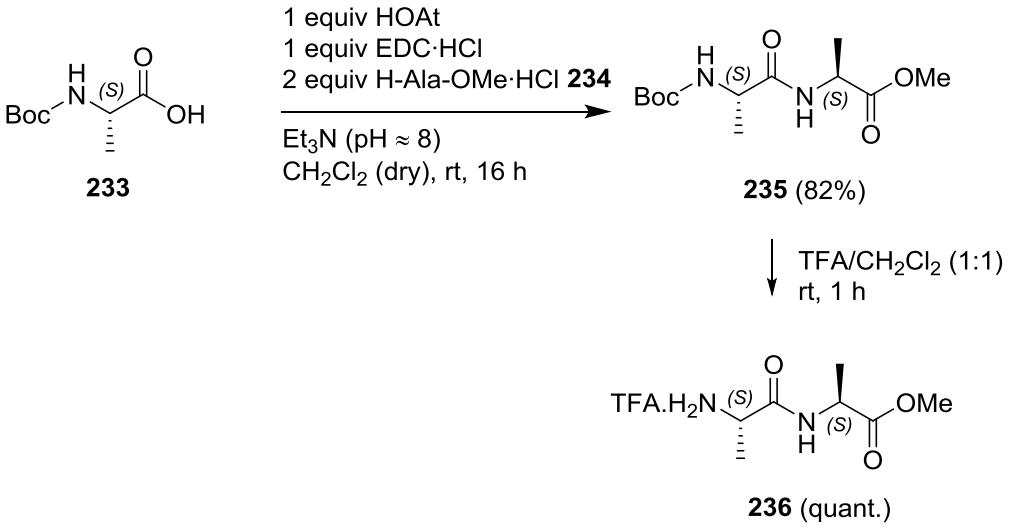
Figure 14

Based on this similarity, it was intended to assess whether the presence of the aminomethyl substituent affects the β-turn/helix induction tendency of the parent Ac_3c residue. To this aim, the tripeptides Cbz-$AMAc_3c$-Ala-Ala-OMe **231** and Cbz-Ala-$AMAc_3c$-Ala-OMe **232** were synthesized by classical methods of peptide synthesis in solution.

The syntheses of model peptides described within this paragraph were performed at the University of Padova (Italy) during a research stay under the supervision of Prof. F. Formaggio.

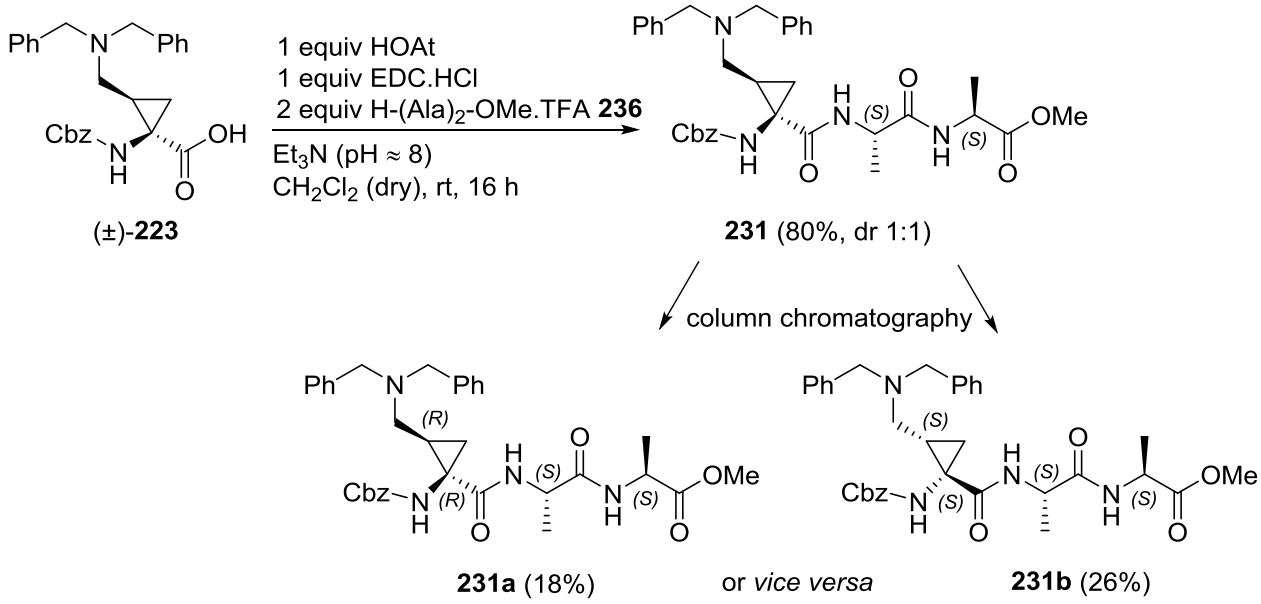
3.4.1 Synthesis of Cbz-$AMAc_3c$-Ala-Ala-OMe tripeptide

In the first step Boc protected alanine **233** was coupled with alanine methyl ester hydrochloride **234** by using the HOAt/EDC activation method to afford Boc-$(Ala)_2$-OMe **235** in 82% yield (Scheme 57).



Scheme 57

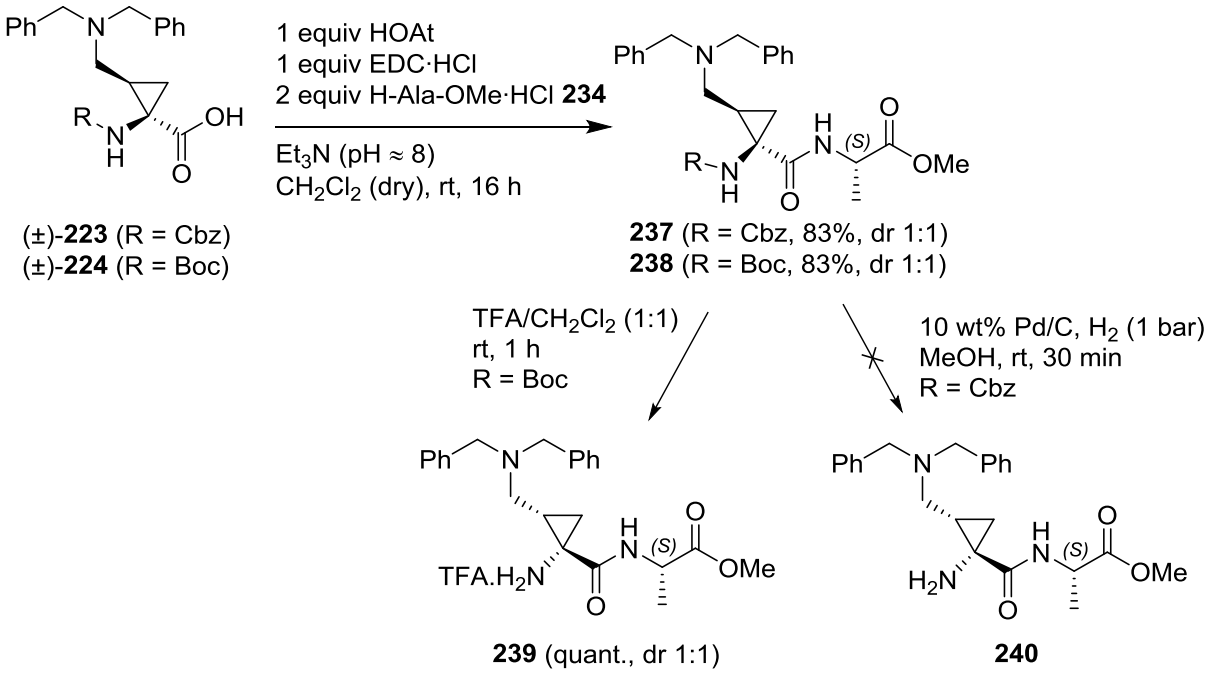
The *N*-*t*-butoxycarbonyl protecting group of dipeptide **235** was subsequently removed by reaction with trifluoroacetic acid in dichloromethane and the obtained TFA salt **236** was used without further purification in a final HOAt/EDC-mediated coupling reaction with *N*-benzyloxycarbonyl-protected carboxylic acid (±)-**223** to give the desired tripeptide Cbz-AMAc$_3$c-Ala-Ala-OMe **231** in 80% yield as a 1:1 mixture of diastereomers (Scheme 58). Both diastereomers were separated by column chromatography to give the enantiomerically pure compounds **231a** and **231b** in 18% and 26% yield, respectively. Unfortunately, the absolute configuration of both diastereomers has not been determined yet.



Scheme 58

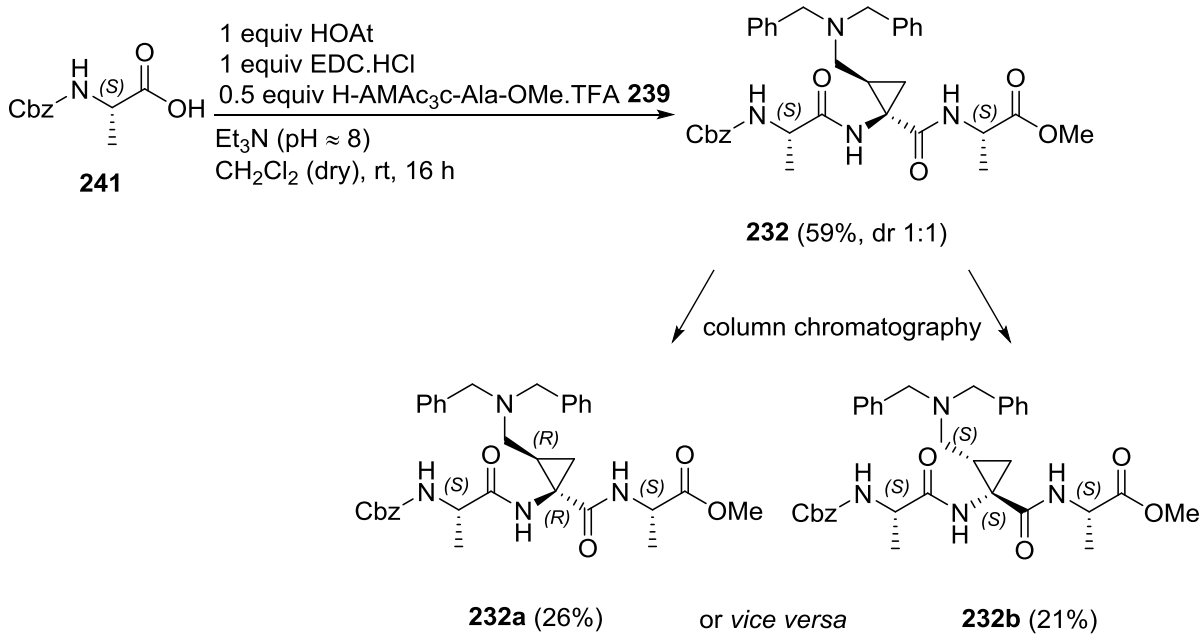
3.4.2 Synthesis of Cbz-Ala-AMAc$_3$c-Ala-OMe tripeptide

Cbz-AMAc$_3$c-OH (±)-**223** was coupled with alanine methyl ester hydrochloride **234** to afford Cbz-AMAc$_3$c-Ala-OMe **237** in 83% yield as a 1:1 mixture of diastereomers which could not be separated *via* column chromatography (Scheme 59). Since both diastereomers of the previously synthesized tripeptide **231** were separable *via* column chromatography, it was believed that also in this case, the introduction of an extra alanine fragment would lead to the formation of separable diasteromers and the mixture of dipeptides **237** was used in a next coupling reaction. Subsequent removal of the *N*-benzyloxycarbonyl protecting group to yield dipeptide **240** by catalytic hydrogenation failed however, leading to a complex reaction mixture in which debenzylation of dipeptide **237** also occured according to LC-MS and ^{1}H NMR results. The strategy was changed and this time, Boc-protected dipeptide Boc-AMAc$_3$c-Ala-OMe **238** was prepared in 83% yield. Again a 1:1 mixture of diastereomers, not separable *via* column chromatography, was obtained.



Scheme 59

The *N*-Boc protecting group was removed by treatment with TFA in CH_2Cl_2 and the obtained salt **239** was coupled with Cbz-protected alanine **241** to afford the desired tripeptide Cbz-Ala-AMAc$_3$c-Ala-OMe **232** in 59% combined yield and 1:1 diastereomeric ratio (Scheme 60). Both diastereomers again were separated *via* column chromatography to give the optically active compounds **232a** and **232b**, of which the absolute configuration still needs to be determined, in 26% and 21% yield, respectively.

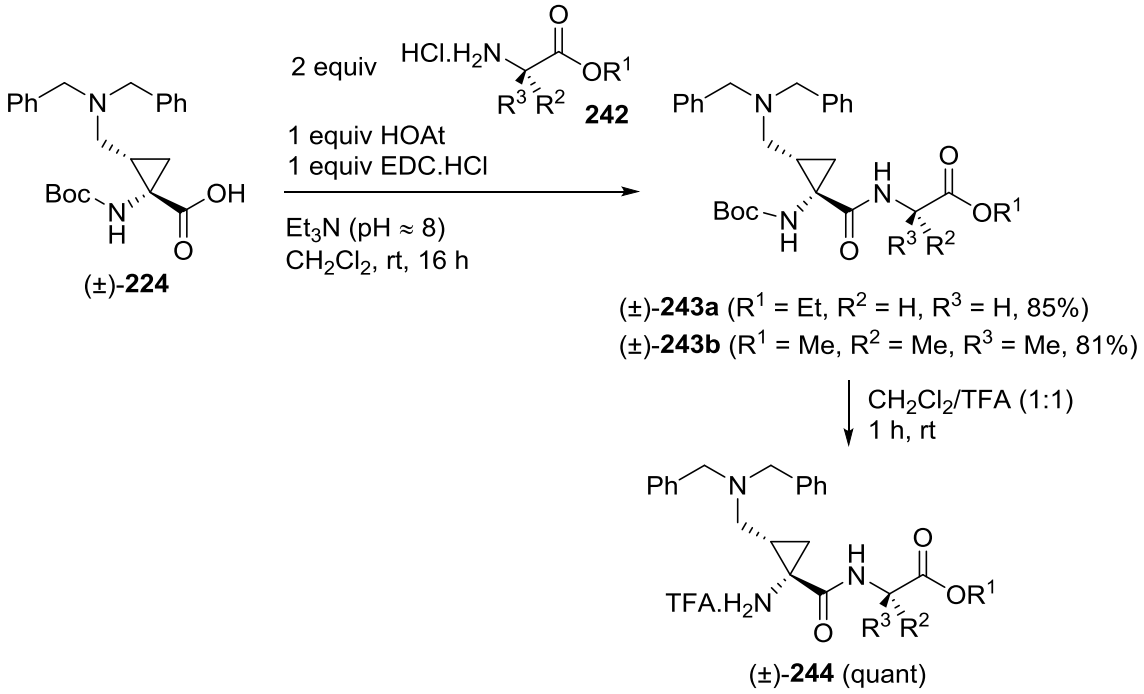


Scheme 60

3.4.3 Synthesis of tripeptides containing glycine and α-aminoisobutyric acid (Aib)

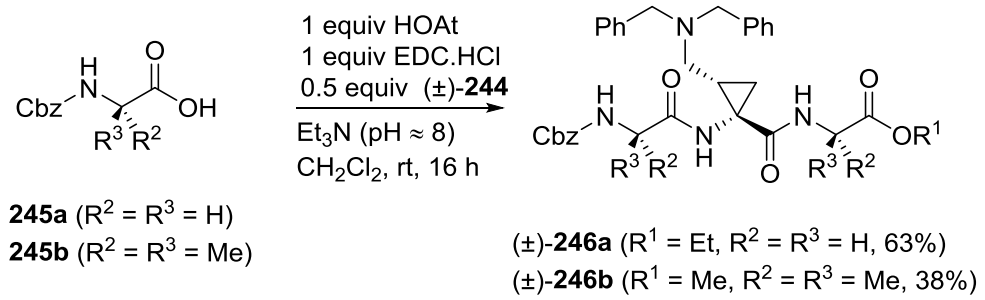
Since the incorporated cyclopropane residue is a racemic mixture of enantiomers, coupling with chiral amino acids leads to the formation of diastereomers, which have to be separable from each other. To avoid this problem, tripeptides containing the achiral amino acids glycine and Aib were also synthesized since the obtained mixtures of enantiomers would still give valuable information about the conformational preferences of the peptides. Furthermore, the strong tendency of Aib peptides to give single crystals would allow a detailed X-ray diffraction analysis of the obtained peptides.[83]

In a first step, Boc-AMAc$_3$c-OH (±)-**224** was coupled with glycine ethyl ester hydrochloride **242a** to provide Boc-AMAc$_3$c-Gly-OEt (±)-**243a** in 85% yield after column chromatography, coupling of Boc-AMAc$_3$c-OH (±)-**224** with 2-aminoisobutyric acid methyl ester hydrochloride H-Aib-OMe.HCl **242b** provided Boc-AMAc$_3$c-Aib-OMe (±)-**243b** in 81% yield (Scheme 61). TFA-mediated deprotection in CH_2Cl_2 of the *N*-Boc protecting group gave TFA-salts (±)-**244**, which were used without further purification in the next coupling step.



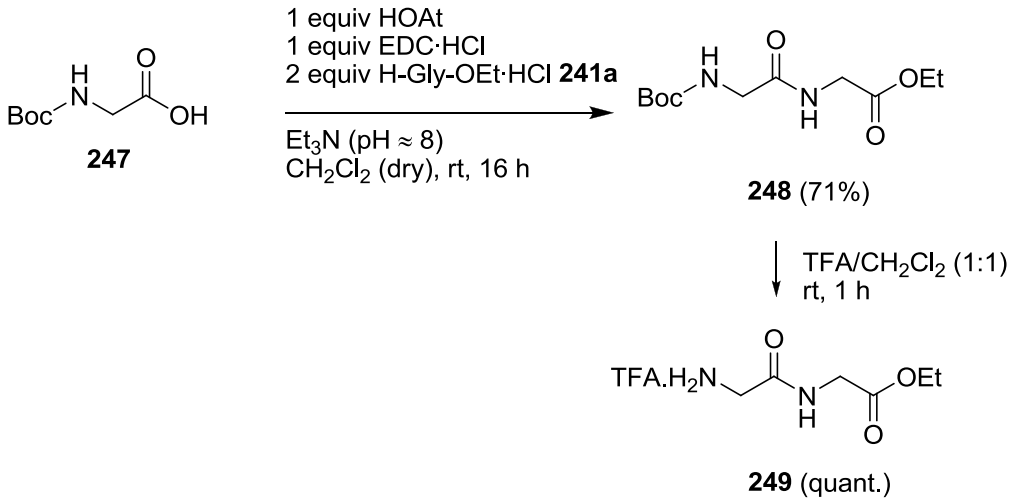
Scheme 61

The desired tripeptides Cbz-Gly-AMAc$_3$c-Gly-OEt (±)-**246a** and Cbz-Aib-AMAc$_3$c-Aib-OMe (±)-**246b** were obtained in 63% and 38% yield, respectively, *via* HOAt/EDC coupling of the obtained TFA-salts (±)-**244** with Cbz-protected glycine **245a** or Aib **245b** followed by purification *via* column chromatography (Scheme 62).



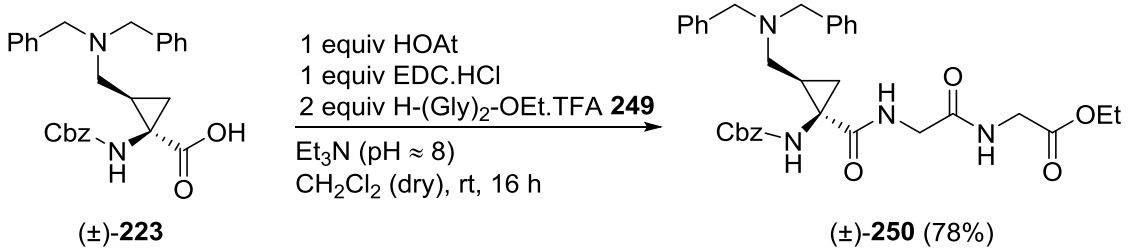
Scheme 62

Coupling of Boc-protected glycine **247** and glycine ethyl ester hydrochloride **242a** *via* the HOAt/EDC activation method afforded the corresponding dipeptide Boc-(Gly)$_2$-OEt **248** in 71% yield (Scheme 63).



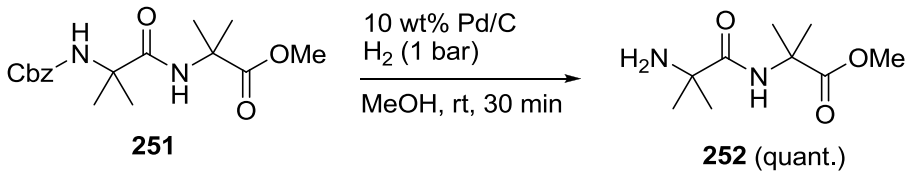
Scheme 63

Again, TFA-mediated deprotection in CH_2Cl_2 of the *N*-Boc protecting group, present in dipeptide **248**, followed by HOAt/EDC coupling of the obtained TFA salt **249** with Cbz-AMAc$_3$c-OH (±)-**223** led to the tripeptide Cbz-AMAc$_3$c-(Gly)$_2$-OEt (±)-**250** in 78% yield after column chromatography (Scheme 64).



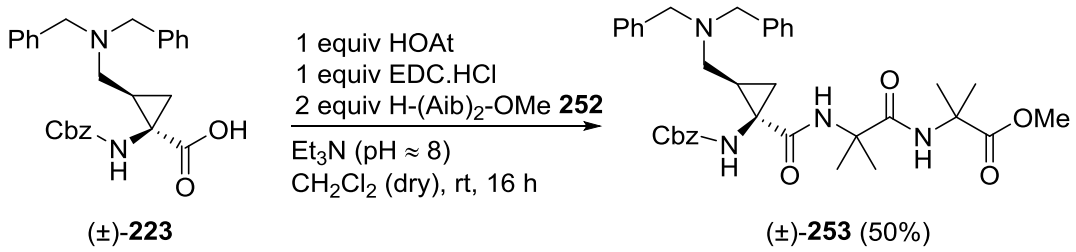
Scheme 64

The *N*-protecting benzyloxycarbonyl group of dipeptide Cbz-(Aib)$_2$-OMe **251**, available at the host institution, was quantitatively removed by catalytic hydrogenation, using an atmospheric pressure of hydrogen gas in the presence of Pd/C in methanol (Scheme 65).



Scheme 65

Having both fragments in hand, a final HOAt/EDC coupling of Cbz-AMAc$_3$c-OH (±)-**223** with deprotected dipeptide H-(Aib)$_2$-OMe **252** afforded Cbz-AMAc$_3$c-(Aib)$_2$-OMe (±)-**253** in 50% yield (Scheme 66).

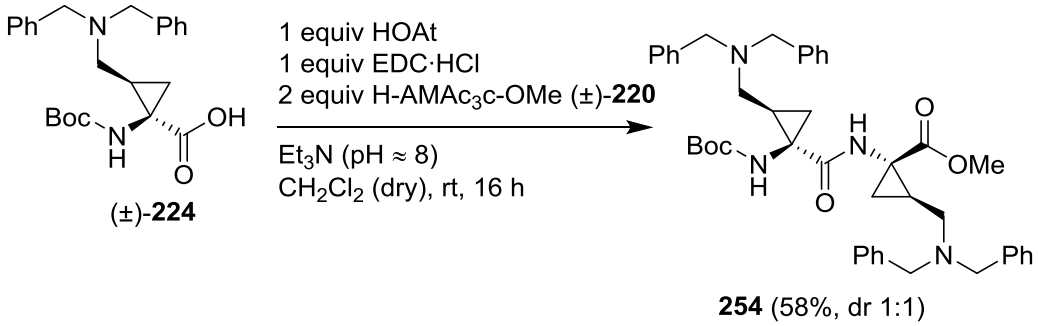


Scheme 66

3.4.4 Attempted synthesis of Cbz-(AMAc$_3$c)$_n$-OMe homopeptides

As the homopeptide sequences would be the most suited for a clear assignment of the conformational preferences of the 2-(aminomethyl)-1-aminocyclopropanecarboxylic acid derivatives, attempts were made to synthesize Cbz-(AMAc$_3$c)$_n$-OMe homopeptides (n = 3-5).

Boc-AMAc$_3$c-OH (±)-**224** was successfully coupled with H-AMAc$_3$c-OMe (±)-**220** using the HOAt/EDC activation method to give the homodipeptide Boc-(AMAc$_3$c)$_2$-OMe **254** in 58% yield as a 1:1 mixture of the diastereomers which were not separable *via* column chromatography (Scheme 67).



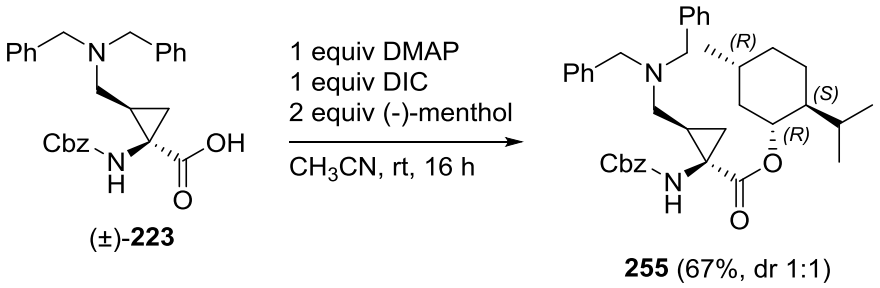
Scheme 67

Coupling with another fragment at this stage would be useless since this would lead to a complex mixture of eight stereoisomers, which would be inseparable for sure. Therefore, the need of enantiomericaly pure starting materials to synthesize these homopeptides is unavoidable and different attempts were undertaken to obtain the enantiopure AMAc$_3$c starting material *via* chiral resolution.

3.4.5 Chiral resolution of 2-(aminomethyl)-1-aminocyclopropanecarboxylic acid derivatives

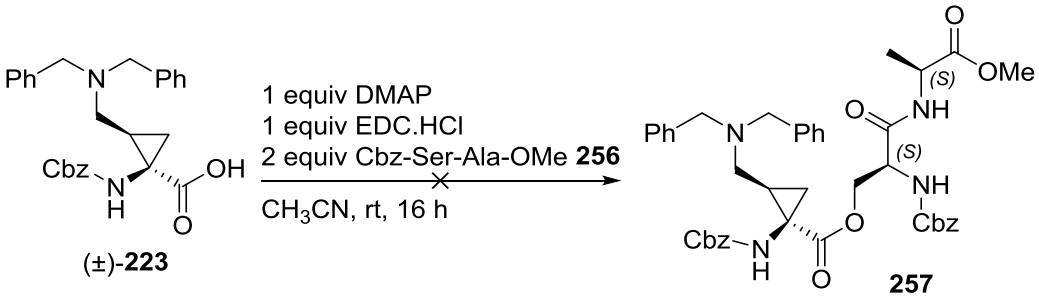
Derivatization of racemic mixtures is possible *via* reaction with optically active reagents, forming pairs of diastereomers that are separable by conventional techniques, such as column chromatography. However, after separation of the diastereomers, it should be possible to obtain the optically pure cyclopropane for further elaboration, thus implying that the coupled optically active

reagents should be readily removable. A first strategy was to couple Cbz-AMAc$_3$c-OH (±)-**223** with a chiral alcohol, separate the obtained diastereomers and finally obtain the enantiopure carboxylic acid **223** after basic hydrolysis of the ester bond. In a first attempt, Cbz-AMAc$_3$c-OH (±)-**223** was coupled with (-)-menthol but unfortunately an inseparable 1:1 mixture of diastereomers **255** was obtained in 67% yield (Scheme 68).



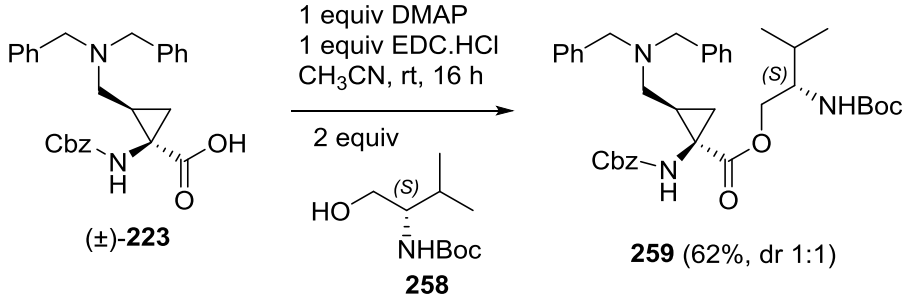
Scheme 68

Since the tripeptides **231** and **232**, containing two extra chiral centra, were separable *via* column chromatography, it was tried to mimic these tripeptides *via* coupling of Cbz-AMAc$_3$c-OH (±)-**223** with the side-chain hydroxyl function of the serine residue in dipeptide Cbz-Ser-Ala-OMe **256**, prepared *via* the HOAt/EDC activation method described above, without success (Scheme 69).



Scheme 69

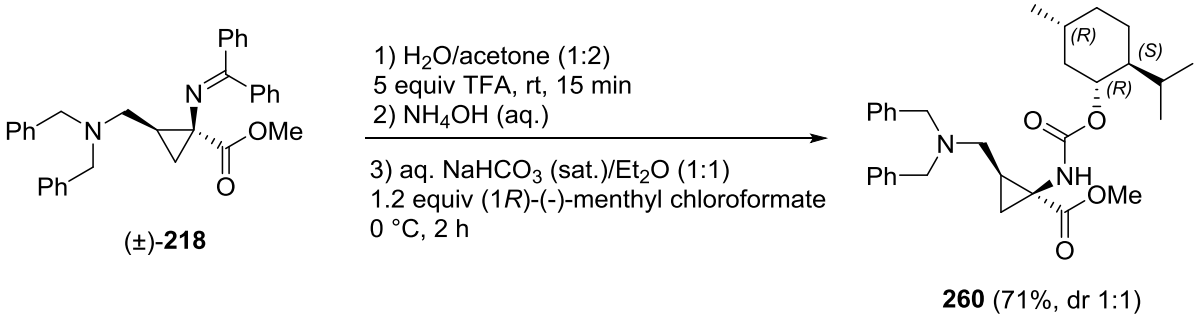
In a final attempt, Cbz-AMAc$_3$c-OH (±)-**223** was coupled with amino alcohol **258** but again an inseparable mixture of diastereomers **259** was obtained (Scheme 70).



Scheme 70

Since the *N*-diphenylmethylidene protecting group in cyclopropane (±)-**218** needs to be replaced by another more appropriate one for further elaboration of the compound, the idea arose to introduce

a chiral protecting group on nitrogen. Indeed, examples exist in literature were diastereomers, *N*-protected with (1*R*,2*S*,5*R*)-(-)-menthyl chloroformate, were separated from each other.[86] Cyclopropane (±)-**218** was deprotected in a first step *via* reaction with TFA and subsequently coupled with (1*R*,2*S*,5*R*)-(-)-menthyl chloroformate to the corresponding carbamate **260** as a 1:1 mixture of diastereomers. Unfortunately again, both diastereomers were not separable *via* column chromatography (Scheme 71).

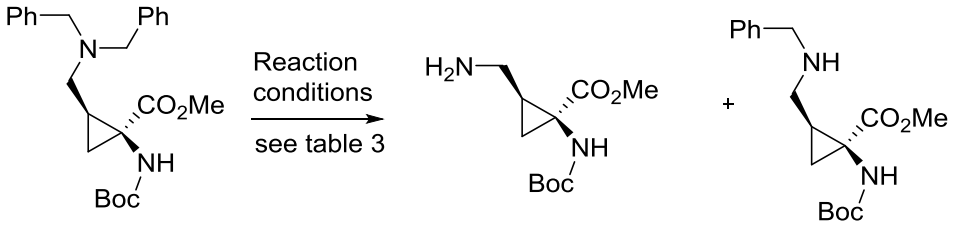


Scheme 71

The first synthesis of carnosadine **11**, described by Shiba *et al.*,[16] involved a resolution step in which two diastereomers **266**, separable by column chromatography, were obtained *via* coupling of a racemic 2-aminomethyl-1-aminocyclopropanecarboxylic acid derivative with chiral (*R*)-(+)-α-methylbenzylamine. In a next step, the amide bond was hydrolyzed again with 6M HCl. Starting from the racemic cyclopropane (±)-**222**, the described compound should be easily accessible and this way it would be possible to resolve both enantiomers.

In a first step, debenzylation of the aminomethyl substituent of cyclopropane (±)-**222** was investigated (Table 3). In a first experiment, conditions that were successful for the deprotection of compound (±)-**225** were applied, however, a mixture of monodebenzylated cyclopropane (±)-**262** and completely deprotected cyclopropane (±)-**261** was obtained (Entry 1). Prolonged reaction time of 16 hours (Entry 2) or application of a higher hydrogen pressure (Entry 3) also did not result in complete deprotection of compound (±)-**222**. Finally, ammonium formate was used as hydrogen source under reflux in methanol in the presence of Pd/C, and this time the deprotected compound (±)-**261** was obtained in 96% yield (Entry 4).

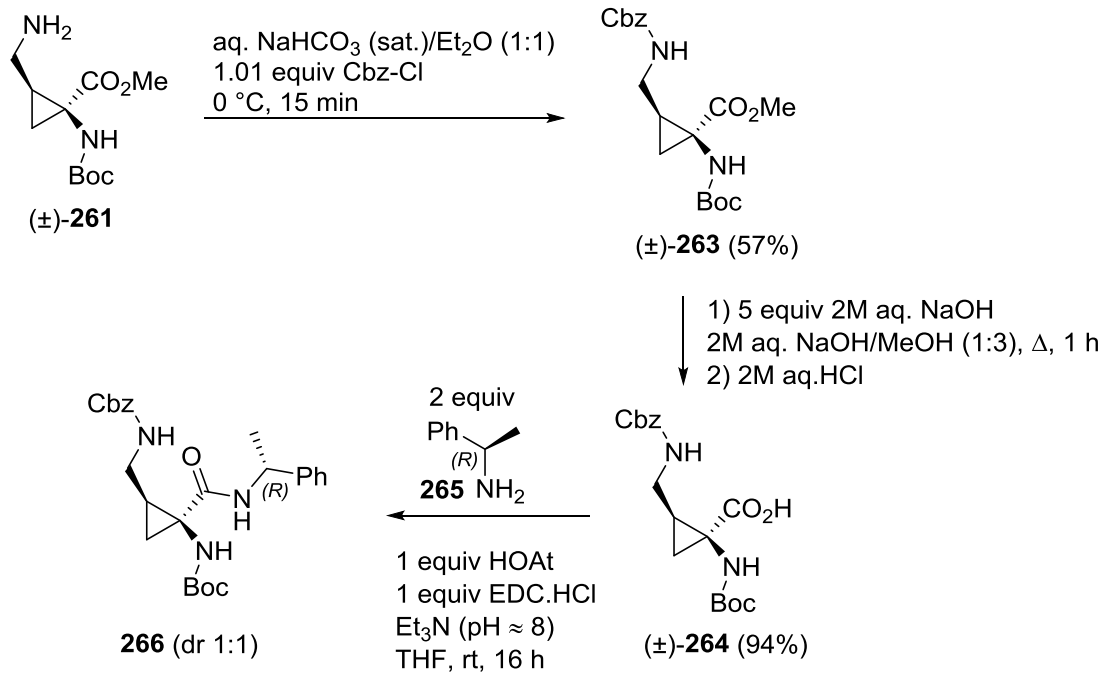
Table 3. Debenzylation of cyclopropane (±)-222



(±)-**222** (±)-**261** (±)-**262**

Entry	Reaction conditions	Result
1	20% Pd/C, H_2 (2 bar), MeOH, rt, 4 h	Mixture of (±)-**261** and (±)-**262**
2	20% Pd/C, H_2 (2 bar), MeOH, rt, 16 h	Mixture of (±)-**261** and (±)-**262**
3	20% Pd/C, H_2, (4.5 bar), MeOH, rt, 5 h	Mixture of (±)-**261** and (±)-**262**
4	5 equiv NH_4HCO_2, 20% Pd/C MeOH, Δ, 30 min	complete deprotection (±)-**261**, 96%

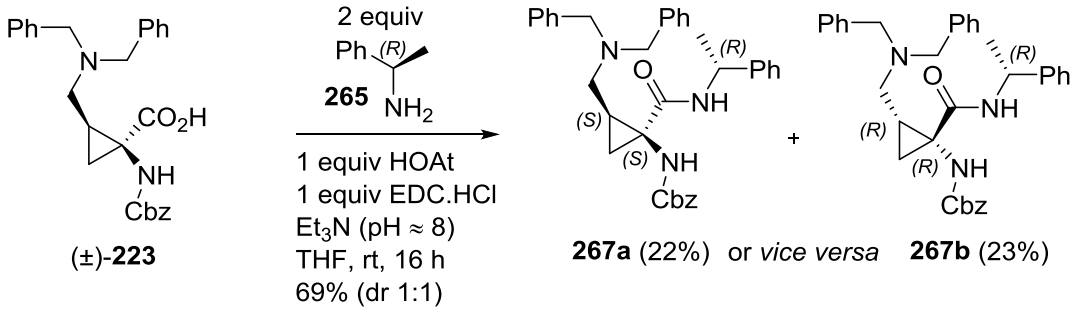
In the following step, the free amine (±)-**261** was protected again upon reaction with benzyl chloroformate in a 1:1 mixture of Et_2O/aq. $NaHCO_3$ (sat.) for 15 minutes at 0 °C to give *N*-Cbz protected cyclopropane (±)-**263** in 57% yield (Scheme 72). Subsequent saponification of the latter compound under alkaline conditions to carboxylic acid (±)-**264**, followed by coupling *via* the HOAt/EDC activation method with (*R*)-(+)-α-methylbenzylamine **265** afforded the same amide **266** as reported by Shiba *et al.* as a 1:1 mixture of diastereomers.[16]



Scheme 72

Indeed both diastereomers were separable *via* column chromatography, unfortunately the compounds were lost during an accident in the lab before they could be analysed.

A closer look at the literature described by Shiba *et al.* revealed however that no data of the resulting diastereomers **266** was available for comparison and so direct determination of the absolute configuration of the obtained compounds **266** would not be possible.[16] Therefore, the previously described synthetic route was abandoned and it was investigated if coupling of cyclopropane (±)-**223** with (*R*)-(+)-α-methylbenzylamine **265** would also lead to a mixture of diastereomers, separable by column chromatography. Indeed, HOAt/EDC-mediated coupling led to a 1:1 mixture of diastereomers **267** in 69% combined yield after a first attempted separation by preparative TLC. Finally, both diastereomers were obtained as enantiopure compounds in 22% and 23% yield, respectively, after additional preparative TLC (Scheme 73). One of the diastereomers was obtained as an amorphous solid and at this moment attempts are made to obtain single crystals, suitable for X-ray diffraction analysis to determine the absolute configuration of the compounds.



Scheme 73

Currently, the conformational preferences of the synthesized tripeptides are being investigated at the host institution. Attempts to grow single crystals are being made and crystal-state (X-ray diffraction) analyses and solution (^{1}H-NMR and infrared) investigations will be performed to reveal the conformational preferences induced by the C^{α}-tetrasubstituted amino acid residues .

However, preliminary results obtained from an IR absorption investigation, indicate that the trisubstituted nitrogen of the aminomethyl substituent may in fact act as a hydrogen-bond acceptor. The IR absorption study was performed in $CDCl_3$ and the frequency interval of 3550-3200 cm^{-1} (Amide A band), related to the stretching vibrations of the N-H bonds belonging to the urethane and amide groups, was analyzed. It is generally assumed that in $CDCl_3$ solvated NH groups (the so-called free NHs) resonate at wave numbers higher than 3400 cm^{-1}, whereas H-bonded NH groups resonate at lower wavelengths.[87] The spectrum of the synthesized dipeptide Cbz-AMAc_3c-Ala-OMe **237** (Figure 15), shows an absorption band at 3428 and a smaller one at 3378. As the dipeptides cannot form a β-turn, it must be assumed that a non-classical, weak H-bond is present. To exclude the possibility whether the band of the H-bonded NH is due to intermolecular interactions, the effect of dilution was studied and Figure 16 shows the spectra of Cbz-AMAc_3c-Ala-OMe **237** at two concentrations (the 10-fold dilution is counterbalanced by a 10-fold increase of the cuvette pathlength). As only moderate dilution effects were observed, the H-bond is likewise intramolecular. The same behaviour was observed for all other dipeptides.

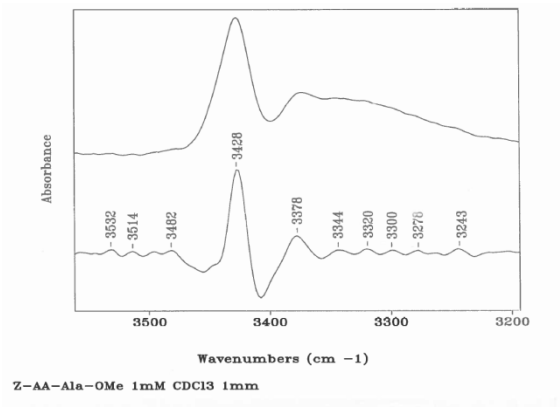


Figure 15. IR absorption spectrum of dipeptide 237 in $CDCl_3$ solution at 1mM peptide concentration, the bottom line is the inverted second derivative

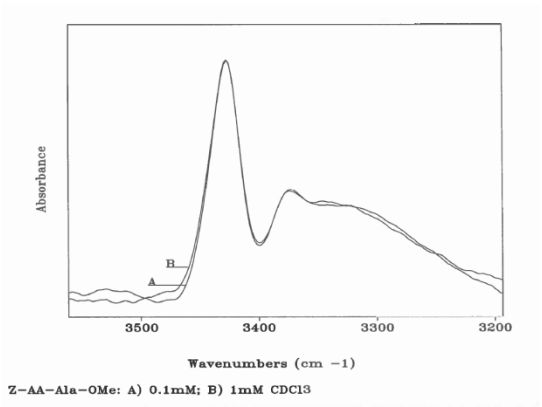


Figure 16. IR absorption spectra of dipeptide 237 in $CDCl_3$ solution at 0.1mM (A) and 1mM (B) peptide concentration

In conclusion, 2-aminomethyl-substituted 1-aminocyclopropane-1-carboxylic acid derivatives were used for the synthesis of model peptides in good yield, using classical methods of peptide synthesis in solution. However, since the incorporated cyclopropane residue is a racemic mixture of enantiomers, the synthesis of stereochemically pure homopeptides was not possible. Coupling of this cyclopropane with a chiral amine afforded separable diastereomers **267** of which the absolute stereochemistry still needs to be determined. Having both diastereomers in hand, hydrolysis of the amide function should be investigated to obtain the enantiopure cyclopropane residue **223**. Subsequently, these enantiopure cyclopropanes can be used for the synthesis of optically active homopeptides. Elucidation of the preferred secondary structure of peptides containing this conformationally constrained cyclopropane residue could make this C^{α}-tetrasubstituted α,γ-diamino acid a usefull scaffold for the design of peptidomimetic drugs.

3.5 Synthesis of 3-aryl-3-pyrrolines and 3-arylpyrroles *via* spontaneous rearrangement of *N*-sulfinyl 2-aryl-2-vinylaziridines

Functionalized aziridines are versatile intermediates in the synthesis of acyclic nitrogen-containing compounds and azaheterocycles *via* cleavage of the carbon–nitrogen or carbon–carbon bond and *via* elaboration of functionalized substituents.[88] As such, a strong interest exists to obtain a better understanding of the reactivity of aziridines which depends strongly on the substitution pattern of the aziridines and the reaction conditions.[89] The further development of aziridine-mediated synthesis of functionalized heterocycles, especially nitrogen-containing five-membered heterocycles,[90] relies on the availability of highly substituted chiral aziridines and the ability to control their further transformations in the desired way.[91] Vinylaziridines are mostly synthesized by addition of a nitrene to a diene, addition of an allylic ylid to an imine or cyclization of unsaturated amino alcohols,[92] and are increasingly being utilized as reactive building blocks in organic synthesis,[24,88e] *via* nucleophilic

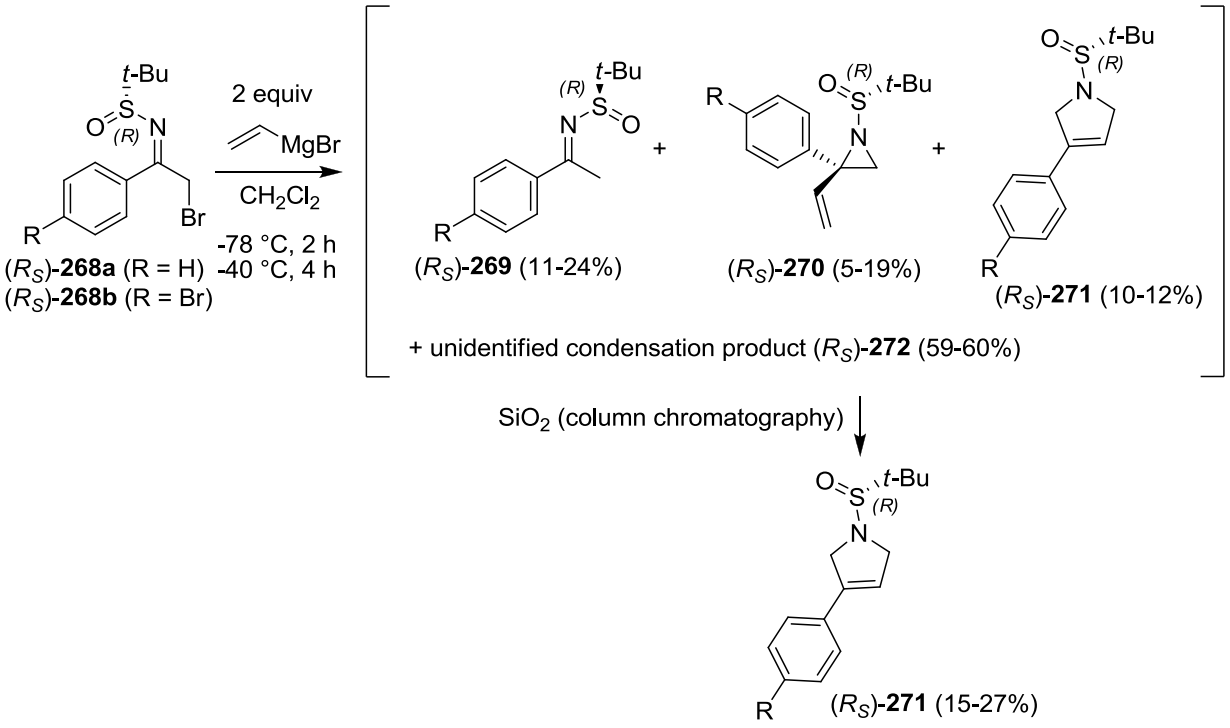
ring opening,[93] and *via* rearrangements toward different azaheterocycles.[94] The rearrangement of 2-vinylaziridines to pyrrolines typically requires thermal (180 °C), nucleophilic (HBr), or metal-promoted conditions.[92] The rearrangement usually yields 3-pyrrolines *via* C–N bond fission,[35,94g,94l,95] but ring expansion to 2-pyrrolines *via* C–C bond cleavage of specifically substituted 2-vinylaziridines is known as well.[94m,96] More specifically, 3-aryl-3-pyrrolines are of significant biological interest as mechanism-based inactivators or substrates of amine oxidases.[97] Moreover, the corresponding 3-arylpyrroles act as reversible competitive inhibitors of monoamine oxidase B.[98] Besides the aforementioned HBr promoted rearrangement of 2-aryl-2-vinylaziridines,[95b] ring-closing metathesis (RCM),[99] Suzuki coupling reactions,[100] ring contraction of 4-aryl-1,2,5,6-tetrahydropyridines,[101] and dehydration of 3-aryl-3-pyrrolidinols,[97d,102] have also been reported as alternative methods for the preparation of 3-aryl-3-pyrrolines.

Inspired by the work of Davis[103] and Ellman,[22a,104] on the use of *N*-sulfinyl imines for the synthesis of a variety of nitrogen containing compounds,[22b,105] our group and others have established the importance of α-halogenated *N*-tert-butanesulfinyl imines in the synthesis of chiral aziridines, including vinylaziridines.[25b,69b,106] Addition of various ylids across enantiopure *N*-sulfinyl imines, provided optically active 2(,2)-(di)substituted 3-vinylaziridines as well.[107] Noteworthy, none of the reported chiral *N*-sulfinyl vinylaziridines have a second substituent on the carbon atom bearing the vinyl group. Recently, however, a synthesis of chiral *N*-sulfinyl 2-alkyl- and 2-allyl-2-arylaziridines *via* Grignard addition across aromatic α-chloroketimines was developed by our research group.[106i] Therefore, it was envisaged that, using the latter method, unreported chiral *N*-sulfinyl 2-aryl-2-vinylaziridines should become accessible as well and would represent suitably substituted activated vinylaziridines for rearrangement to 3-aryl-3-pyrrolines under mild conditions.

3.5.1 Addition of alkenylmagnesium bromides across aromatic *N*-sulfinyl α-halo ketimines

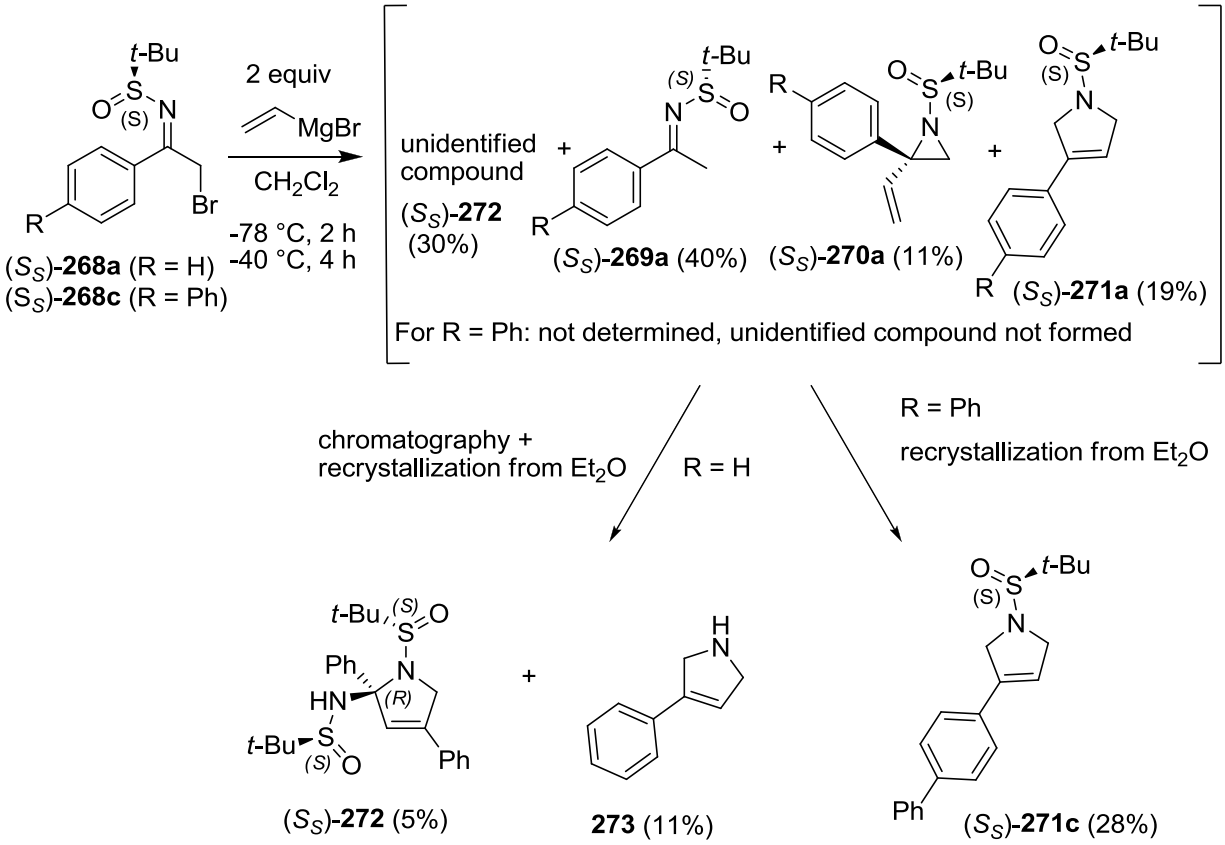
Previous research in our research group has shown that reaction of aromatic α-halo *N*-(*tert*-butanesulfinyl)imines (R_S)-**268**, synthesized in 75-90% yield *via* condensation of α-halo ketones with (R_S)-*tert*-butanesulfinamide and $Ti(OEt)_4$ in tetrahydrofuran,[25b] with two equivalents of vinylmagnesium bromide in CH_2Cl_2 at -78 °C for two hours, followed by four hours at –40 °C, led to reaction mixtures of which analysis of the ^1H NMR spectrum (300 MHz, $CDCl_3$) allowed the identification of 11–24% of dehalogenated imines (R_S)-**269**,[108] 5–19% of 2-aryl-2-vinylaziridines (R_S)-**270**, and 10–12% of 3-aryl-3-pyrrolines (R_S)-**271** together with a large amount (59-60%) of an unidentified condensation product (R_S)-**272** (Scheme 74). However, purification by chromatography on silica gel afforded 3-aryl-3-pyrrolines (R_S)-**271** in 15–27% yield, which led to the assumption that

the chiral *N*-sulfinyl 2-aryl-2-vinylaziridines (R_S)-**270** rearranged, with loss of the resulting stereogenic center, to the 3-aryl-3-pyrrolines (R_S)-**271** during the purification step.



Scheme 74

In order to resolve the structure of the unknown compound (R_S)-**272**, obtained in 59-60% yield, several attempts were made to isolate it from the crude reaction mixtures. The reaction was repeated with (S_S)-α-bromoketimine (S_S)-**268a** and again the unidentified compound (S_S)-**272** was formed in 30% yield, next to 40% of the dehalogenated imine (S_S)-**269a**, 11% of 2-aryl-2-vinylaziridine (S_S)-**270a** and 19% of 3-aryl-3-pyrroline (S_S)-**271a** (based upon ^{1}H NMR analysis of the crude reaction mixture). After column chromatography, followed by recrystallization from Et_2O, the unknown condensation product (S_S)-**272** was isolated in a disappointing yield of only 5%, next to the deprotected 3-aryl-3-pyrroline **273** in 11% yield (Scheme 75).



Scheme 75

The structure of the unknown condensation product was proven to be 3-pyrroline (S_S)-**272** *via* X-ray diffraction analysis (in collaboration with Prof. K. Van Hecke, Inorganic and Physical Chemistry, Ghent University, Belgium) (Figure 17).

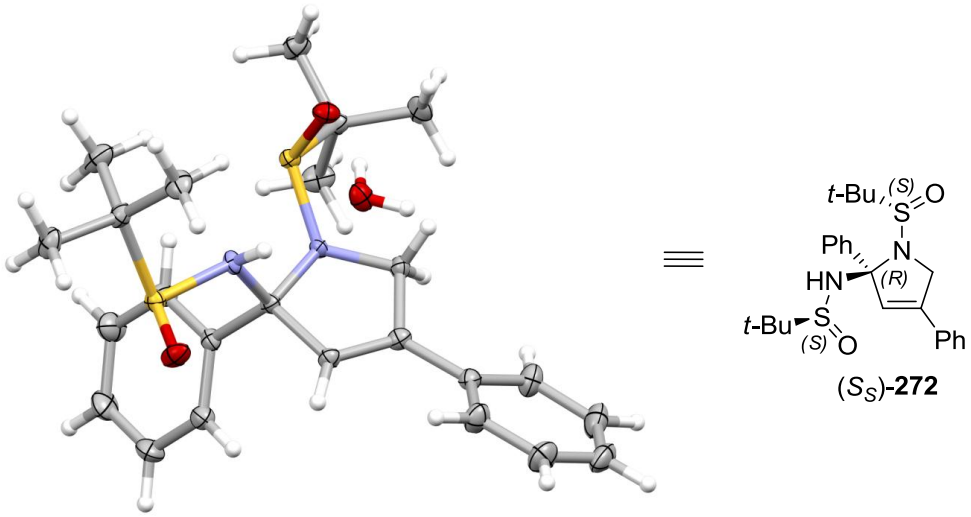


Figure 17. X-ray diffraction analysis of 3-pyrroline (S_S)-272

As can be seen from figure 17 and 18, water is contained within the crystal structure, connecting the different molecules *via* hydrogen bonding.

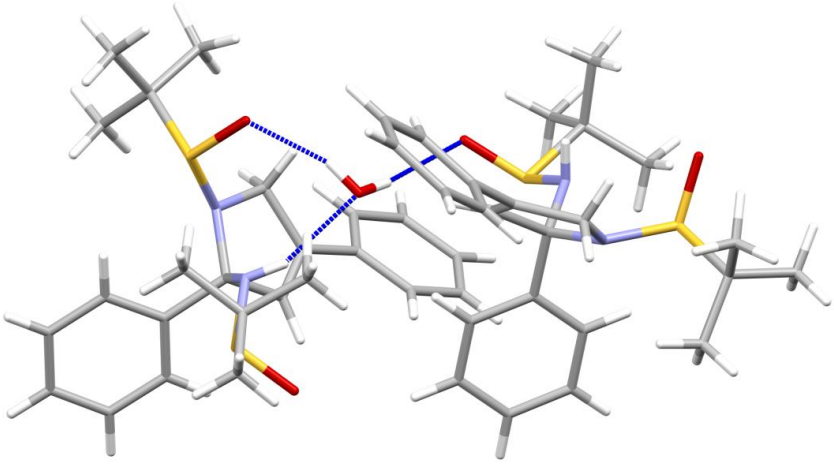
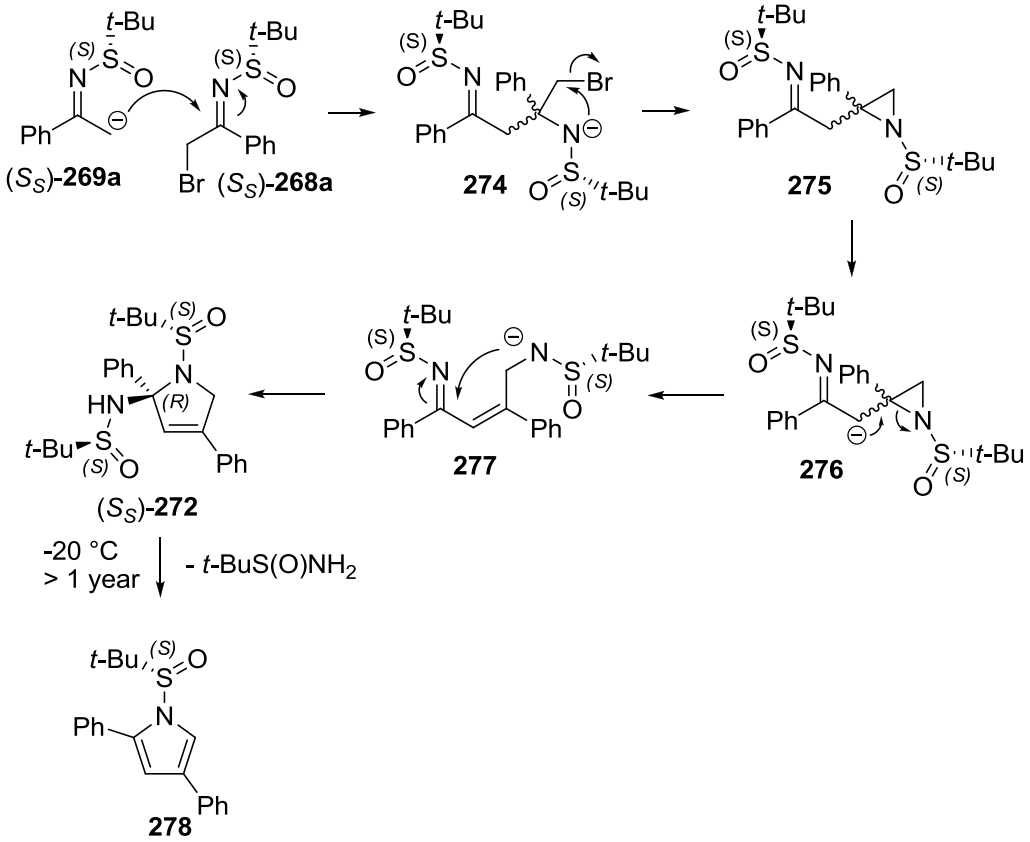


Figure 18. Hydrogen bonding with water in the crystal structure of 3-pyrroline (S_S)-272

The formation of 3-pyrroline (S_S)-**272**, can be rationalized *via* initial formation of the dehalogenated imine (S_S)-**269a**. The reduction of imine (S_S)-**268a** can be explained through β-hydride transfer from the Grignard reagent, in competition with a halogen-metal exchange reaction, which converts the α-halo imine to the corresponding Grignard reagent. Protonation of the reaction mixture then gives the dehalogenated product.[109] Subsequent deprotonation, followed by Mannich-type addition across the starting material (S_S)-**268a** results in the formation of aziridine **275**, which is then ring expanded to the corresponding 3-pyrroline upon second deprotonation, aziridine ring opening and cyclization with exclusive formation of the (2*R*)-isomer (S_S)-**272** (Scheme 76).



Scheme 76

Upon storage in the freezer for a longer period however, compound (S_S)-**272** spontaneously underwent 1,4-elimination of *tert*-butanesulfinamide with formation of the corresponding pyrrole **278**, of which the structure was also confirmed by X-ray diffraction analysis (Figure 19).

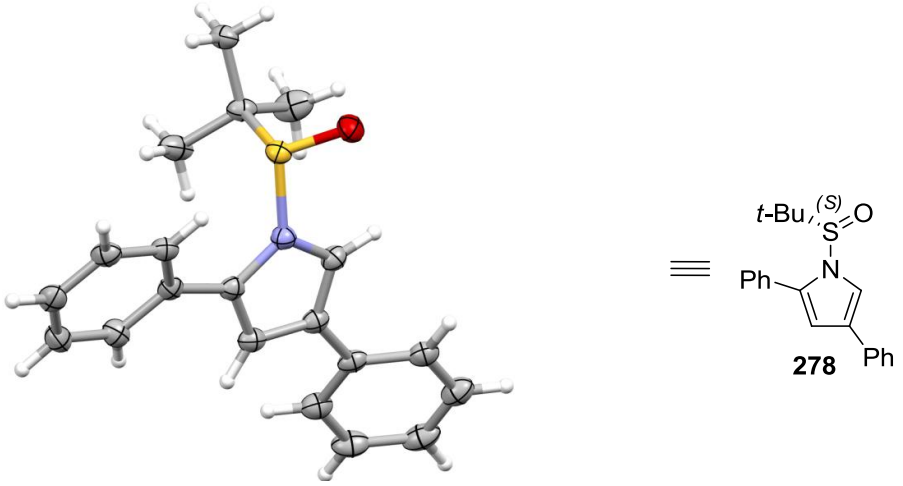
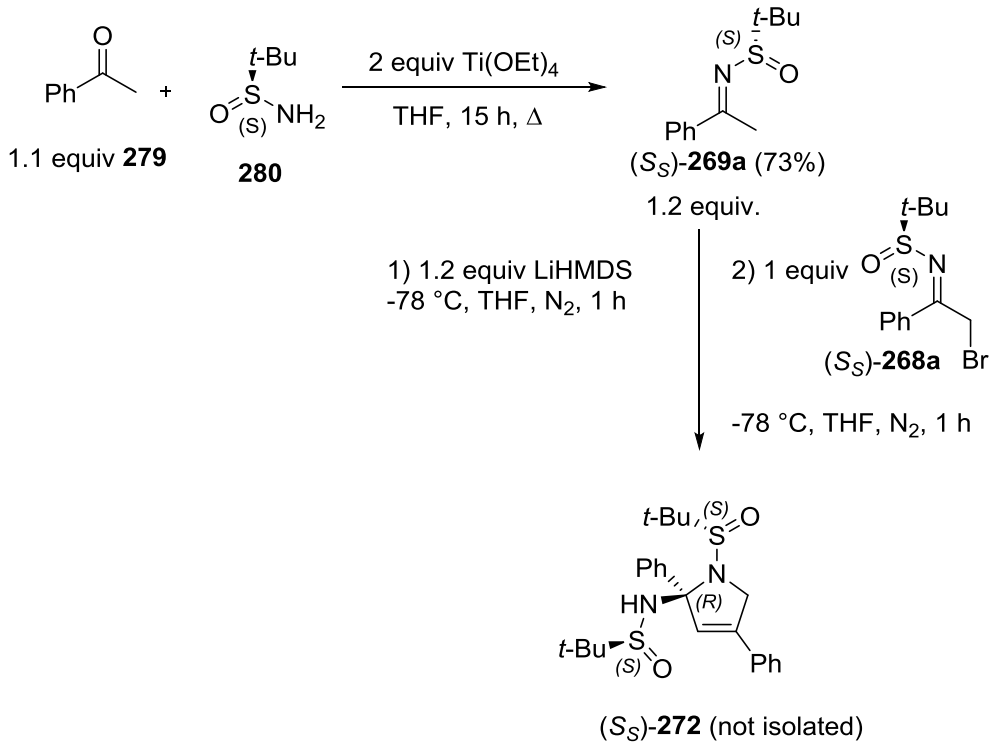


Figure 19. X-ray diffraction analysis of pyrrole 278

In an attempt to isolate the resulting 3-pyrroline (S_S)-**272** in higher yield, *p*-phenylphenyl-substituted *N*-sulfinyl ketimine (S_S)-**268c** was synthesized *via* the previously reported procedure in 39% yield.

Reaction of the latter compound was performed with vinylmagnesium bromide under the same conditions (Scheme 75), hoping the desired product would be easily crystallized from the crude mixture due to the presence of the extra phenyl substituent. Investigation of the crude reaction mixture (^{1}H NMR), however, indicated that the condensation product was not formed, and only 3-pyrroline (S_S)-**271c** was isolated in 28% yield after recrystallization from Et_2O.

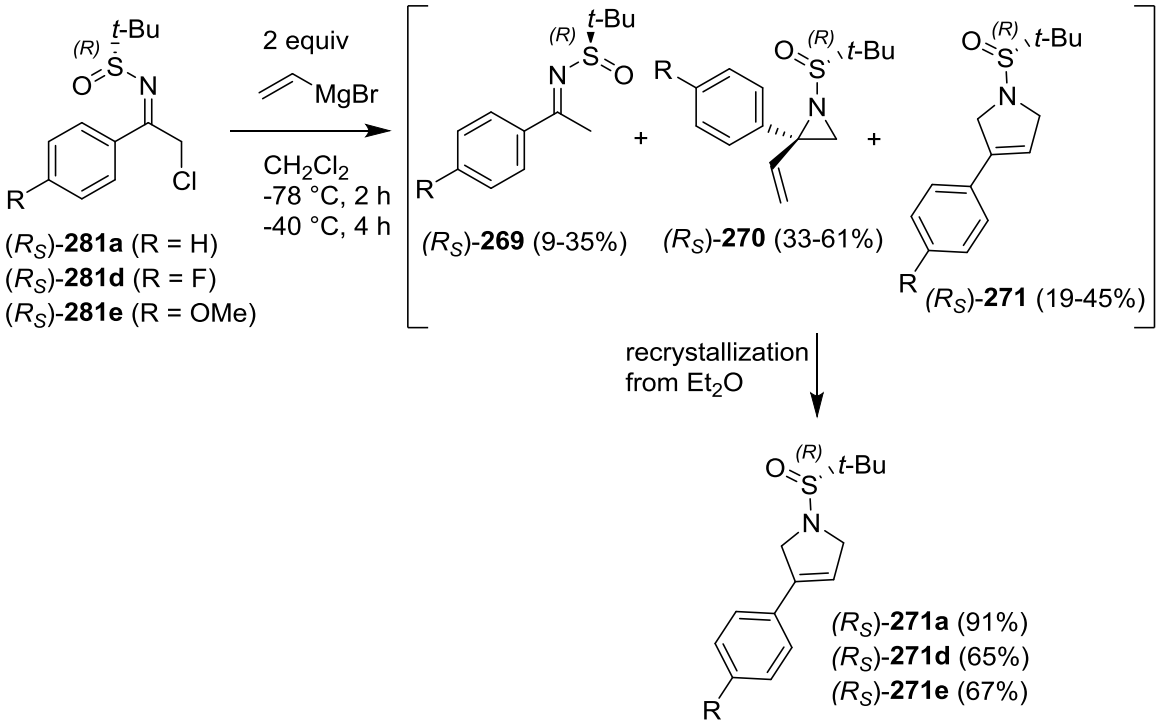
To verify the proposed mechanism for the formation of 3-pyrroline (S_S)-**272**, imine (S_S)-**269a** was synthesized in 73% yield following a literature procedure (Scheme 77).[110] The compound was deprotonated with LiHMDS in THF at -78 °C for one hour and subsequently reacted with α-bromoketimine (S_S)-**268a** for one hour at -78 °C. Comparison of the ^{1}H NMR spectra of the crude reaction mixture with those of the starting materials and the desired product (S_S)-**272** indicated that, next to unreacted starting materials, a significant amount of condensation product (S_S)-**272** was formed. Unfortunately all attempts to isolate it in pure form from the crude reaction mixture failed.



Scheme 77

On the other hand, when two equivalents of vinylmagnesium bromide were added to α-chloroketimines (R_S)-**281** under the same reaction conditions, only three products were observed in the crude reaction mixtures (Scheme 78). The ^{1}H NMR spectrum indicated the presence of 9–35% of dehalogenated imines (R_S)-**269**, accompanied by 33–61% of 2-aryl-2-vinylaziridines (R_S)-**270** and 19–45% of 3-aryl-3-pyrrolines (R_S)-**271**, before purification. After recrystallization of the reaction

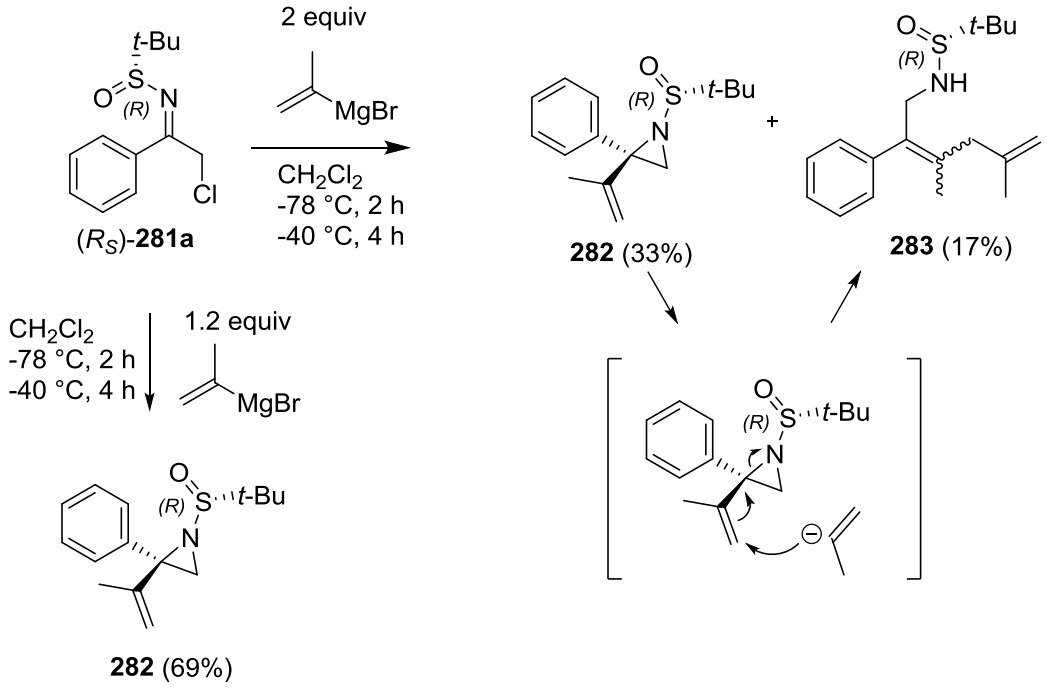
mixtures from diethyl ether no 2-aryl-2-vinylaziridines were obtained, but 3-aryl-3-pyrrolines (R_S)-**271** were isolated in 65–91% yield.



Scheme 78

To extend the scope of the Grignard addition reaction across aromatic ketimines **281**, the addition of other alkenylmagnesium bromides was evaluated. The outcome of the reaction proved to depend highly on the substitution pattern of the Grignard reagent.

In a first experiment, ketimine (R_S)-**281a** reacted with two equivalents of isopropenylmagnesium bromide in CH_2Cl_2 for two hours at -78 °C, followed by four hours at -40 °C (Scheme 79). This time, 2-aryl-2-isopropenylaziridine **282** was isolated as a stable compound in moderate yield, together with the nonconjugated aminodiene **283** in 17% yield. The formation of the latter product can be rationalized by S_N2' ring opening of aziridine **282** with the excess of isopropenylmagnesium bromide and demonstrates the tendency of 2-alkenyl-2-arylaziridines to react *via* C–N bond cleavage. In an attempt to prevent the formation of diene **283** and to improve the yield of aziridine **282**, only a small excess of 1.2 equivalents of isopropenylmagnesium bromide was used in a second experiment. This time, reaction of ketimine (R_S)-**281a** with isopropenylmagnesium bromide afforded 2-phenyl-2-isopropenylaziridine **282** as a single stereoisomer in 69% yield while formation of the aminodinene **283** was not observed.

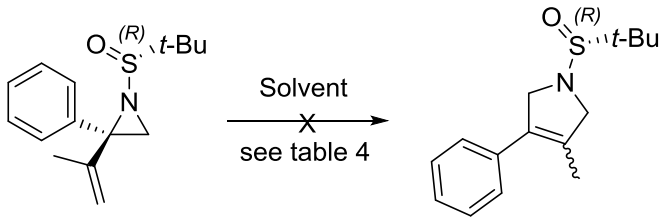


Scheme 79

The stereochemistry of aziridine **282** is assumed to be in analogy with the stereochemistry obtained during the synthesis of similar aziridines from chiral α-chloroaldimines[25b,106a,106c] and is opposite to the one that is predicted *via* the chelation-controlled transition state, which is the general intermediate proposed for non-functionalized *N*-sulfinyl imines.[103-104,111] The reversal of stereochemical outcome of the reaction is attributed to the α-coordinating ability of the chlorine atom and is analogous to the results obtained with other *N*-sulfinylimines containing an α-coordinating group, such as a nitrogen or oxygen atom.[111a,112]

Several attempts were performed to rearrange aziridine **282** to the corresponding pyrroline **284** upon stirring in several solvents (Table 4). Neither reaction at room temperature in Et_2O (Entry 1) nor reaction under reflux (Entry 2-3) and addition of KI (entry 4) resulted in the formation of the desired 3-pyrroline **284**.

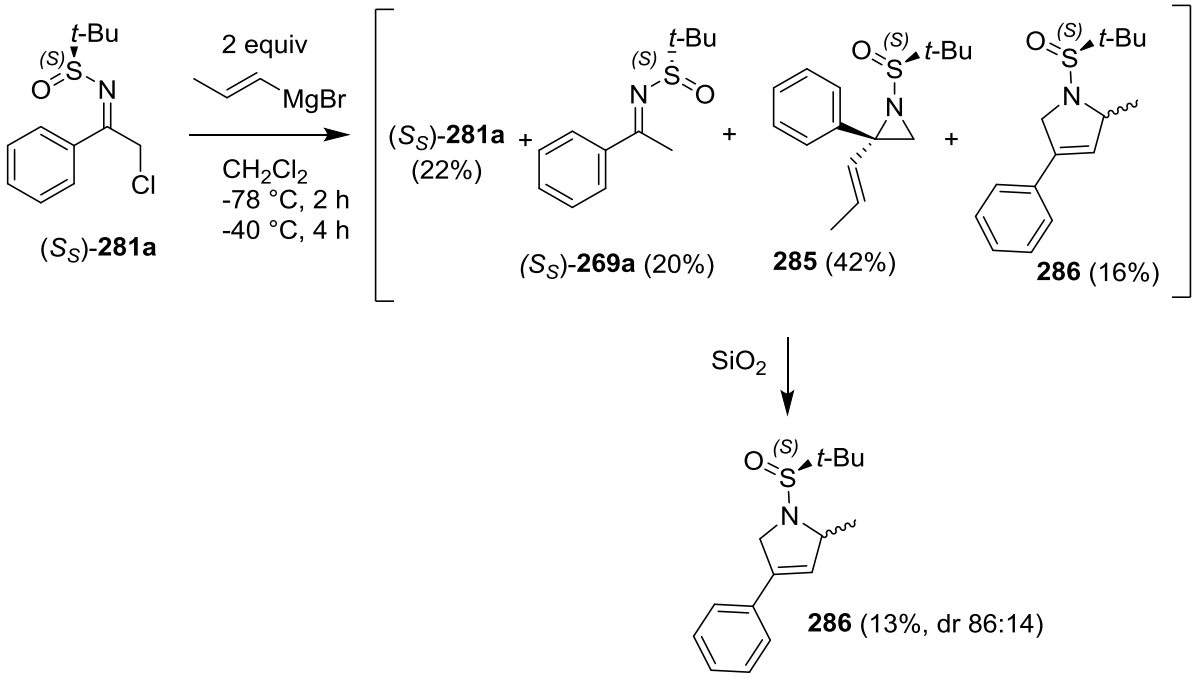
Table 4. Attempted synthesis of pyrroline 284



282 **284**

Entry	Solvent	Reaction conditions	Result
1	Et_2O	rt, 1 h	Recovery of starting material
2	Et_2O	Δ, 1 h	Recovery of starting material
3	THF	Δ, 3 h	Recovery of starting material
4	Toluene	Δ, 1 h	Recovery of starting material
5	Et_2O	Δ, 1 h, 0.2 equiv KI	Recovery of starting material

These results indicate that the rate of rearrangement of 2-alkenylaziridines is influenced by subtle steric effects exerted by the substituents on the double bond. This substitution effect is further demonstrated by the sluggish reaction of (S_S)-*N*-(tert-butanesulfinyl)imine (S_S)-**281a** with 2 equivalents of 1-propenylmagnesium bromide, which resulted in a crude mixture of aziridine **285** as the major product together with pyrroline **286**, dechlorinated imine (S_S)-**269a**, and unreacted imine (S_S)-**281a** (Scheme 80). Purification of this reaction mixture by column chromatography on silica gel proved to be difficult and only the pyrroline **286** (dr = 86:14) was isolated in low yield (13%), while the aziridine **285** was not isolated in pure form.

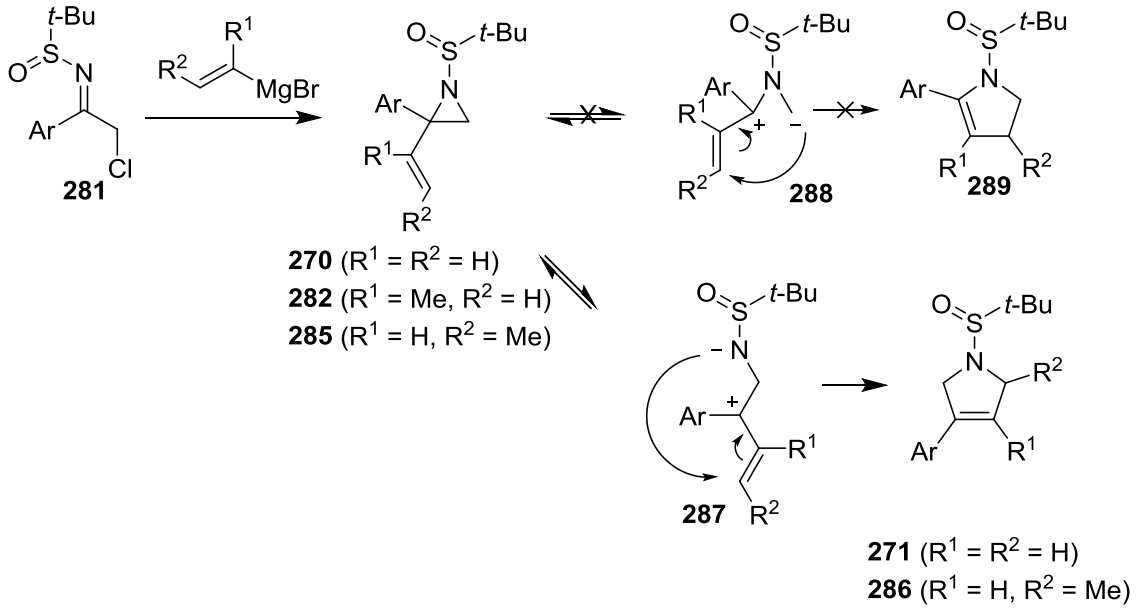


Scheme 80

Upon rearrangement of 2-alkenyl-2-arylaziridines, the formation of 2-aryl-2-pyrrolines **289** *via* C-C bond cleavage should be considered as well (Scheme 81). However, the structural identity of 3-aryl-3-pyrrolines **271** and **286**, was confirmed through comparison of their ^{1}H NMR spectroscopic data with literature data for similar 3-aryl-3-pyrrolines. For the 3-pyrrolines **271**, typical resonance signals in the range of δ = 3.33-4.45 ppm were observed for the two nitrogen-substituted methylene units. The chemical shifts of these methylene units correspond to the reported shifts of related 3-aryl-3-pyrrolines,[94m,97b-d,99c] but differ significantly from the chemical shifts (δ = 2.0–2.6 ppm) of the methylene unit connected to the double bond of the corresponding 2-aryl-2-pyrrolines.[113] This clearly indicated that a CH_2NCH_2 unit is present in the rearranged compounds **271**. Similarly, the ^{1}H NMR spectroscopic data of 3-pyrroline **286** also indicated the presence of a CH_2NCH unit (δ = 3.5–4.2 ppm),[114] and not the NCH_2CH unit that would be present in 2-pyrroline **289** (R^2 = Me). Moreover, the chemical shift of the olefinic methine proton of 3-aryl-3-pyrrolines **271** at around δ = 6 ppm is also in good correspondence with reported values of related 3-aryl-3-pyrrolines,[94m,97b-d,99c] and differs significantly with the reported shifts (δ = 5.2–5.5 ppm) of the enamine proton of the corresponding 2-aryl-2-pyrrolines.[113]

The ready formation of 3-aryl-3-pyrrolines **271** can be explained due to the specific substitution pattern of 2-aryl-2-vinylaziridines **270**. Cleavage of the C–N bond of 2-aryl-*N*-(*tert*-butanesulfinyl)-2-vinylaziridines **270**, due to the high ring strain and the activating electron-withdrawing group on nitrogen, results in a conjugated benzylic carbenium ion **287** (Scheme 81). This zwitterionic

intermediate **287**, in which both the positive and negative charge are stabilized, can ring close *via* an intramolecular nucleophilic attack at the less hindered electrophilic position to the corresponding 3-aryl-*N*-(*tert*-butanesulfinyl)-3-pyrrolines **271**. For the substituted 2-vinylaziridines **282** and **285**, the rearrangement occurs less easily due to steric effects, resulting in either a stable aziridine, for example, compound **282**, or inefficient conversion to the 3-pyrroline, for example, pyrroline **286**. Cleavage of the C–C bond of the aziridines to less stabilized 1,3-dipolar intermediates **288**, which would subsequently result in the formation of 2-pyrrolines **289**, does not occur.

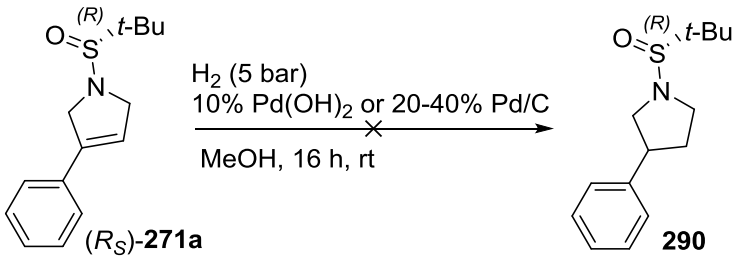


Scheme 81

The structural identity of pyrrolines (R_S)-**271** was further ascertained through exploration of their chemical reactivity.

3.5.2 Attempted hydrogenation of 3-aryl-3-pyrrolines

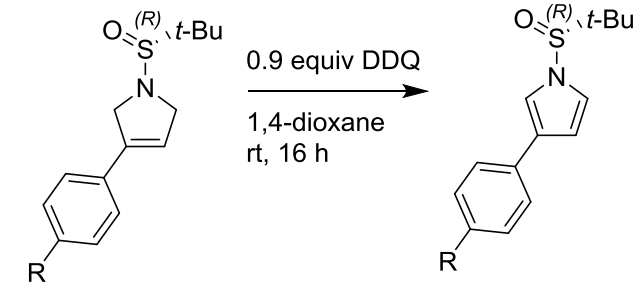
Different 2- and 3-arylpyrrolidines are know in literature. For example, enantiopure 2-aryl-1-(*tert*-butanesulfinyl)pyrrolidines have been synthesized in high yield *via* stereoselective reduction of γ-chloro *N*-sulfinylketimines with lithium triethylborohydride.[115] To be able to compare spectroscopic data, attempts were made to transform 3-pyrroline (R_S)-**271a** to the corresponding pyrrolidine **290** *via* hydrogenation of the double bond (Scheme 82). Both palladium and palladium hydroxide on carbon were used, however, each time the starting material was recovered.



Scheme 82

3.5.3 Oxidation of 3-aryl-3-pyrrolines to 3-arylpyrroles

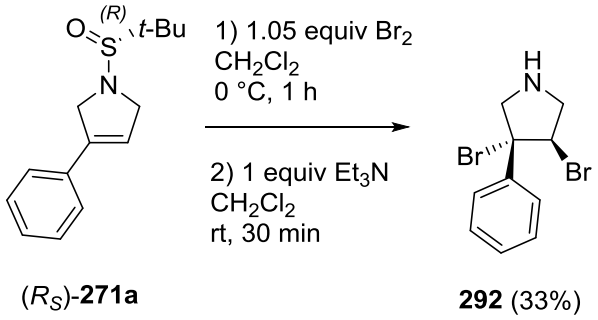
In another experiment, pyrrolines (R_S)-**271** were oxidized with 0.9 equivalents of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in 1,4-dioxane at room temperature for 16 hours to the corresponding 3-arylpyrroles **291** in 69–87% yield (Scheme 83). The resemblance of ^{1}H NMR spectroscopic data of 3-arylpyrroles **291** with data reported in the literature for similar 3-arylpyrroles,[116] and significant differences with data reported in the literature for related 2-arylpyrroles,[117] further confirmed the structural identity of pyrrolines **271**. Both protons of the CHNCH unit, present in 3-arylpyrroles **291** resonate in the range of δ = 7.44-7.79 ppm, while the chemical shift of the other olefinic methine proton is around δ = 5.9 ppm, which is in good correspondence with reported data of related 3-arylpyrroles. Indeed, methine protons of the CHNCH unit present in *N*-tosyl-3-phenylpyrrole also resonate above δ = 7 ppm, while CHCHN resonates below 7 ppm (δ = 6.61 ppm). For *N*-tosyl-2-phenylpyrrole, typical resonance signals were observed below δ = 7 ppm (δ = 6.13 ppm and 6.28 ppm) for the the methine protons of the CHCH unit, while the nitrogen-substituted methine unit resonates above δ = 7 ppm.



Scheme 83

3.5.4 Bromination of 3-phenyl-3-pyrroline

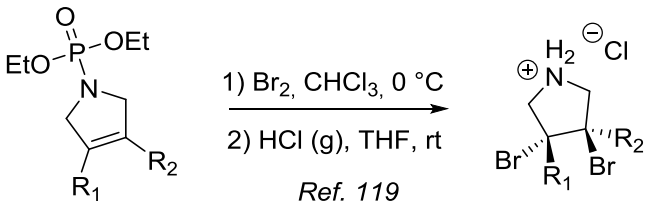
Finally, bromination of 3-phenyl-3-pyrroline (R_S)-**271** afforded the corresponding 3,4-dibromopyrrolidine **292** in moderate yield with spontaneous cleavage of the protective group at nitrogen (Scheme 84).[118]



(R_S)-**271a** **292** (33%)

Scheme 84

A relative *trans*-stereochemistry for the 3,4-dibromopyrrolidine **292**, resulting from a stereospecific *anti*-addition of bromine across the double bond, was assigned.[119] Bromination of related *N*-phosphorylated 3-methyl-3-pyrrolines **293** resulted in the formation of the *trans*-3,4-dibromopyrrolidine hydrochlorides **294** (Scheme 85). The corresponding *cis*-3,4-dibromopyrrolidine hydrochlorides, of which the structure was confirmed by X-ray diffraction analysis were also prepared.



293a (R1 = R2 = H)
293b (R1 = Me, R2 = H)
293c (R1 = R2 = Me)

294a (76%)
294b (66%)
294c (53%)

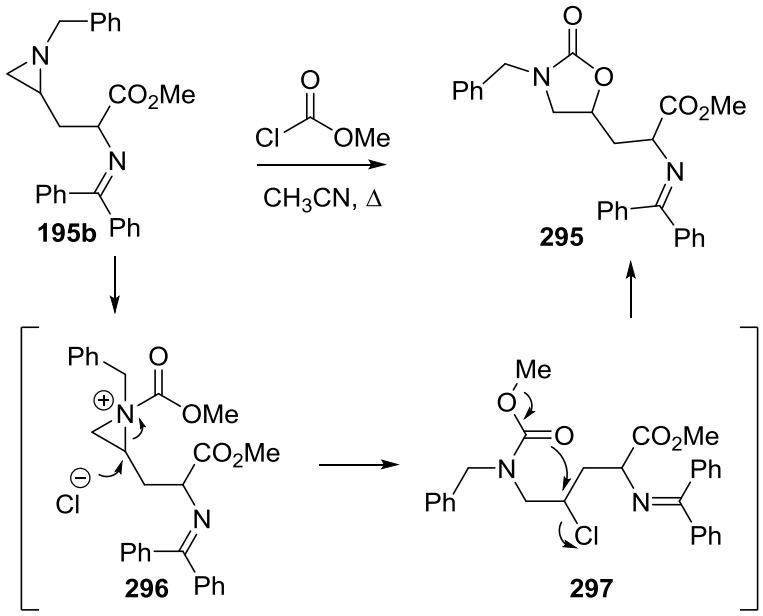
Scheme 85

In conclusion, addition of vinylmagnesium bromide across aromatic *N*-sulfinyl α-chloroketimines afforded *N*-sulfinyl 2-aryl-2-vinylaziridines, which spontaneously rearranged *via* C–N bond cleavage into biologically interesting 3-aryl-3-pyrrolines **271**, underlining the excellent utility of highly substituted activated aziridines in azaheterocyclic synthesis. Reaction with 1-propenylmagnesium bromide proved to be quite sluggish and the corresponding 3-pyrroline **286** was only obtained in low yield. When isopropenylmagnesium bromide was used, *N*-sulfinyl 2-aryl-2-vinylaziridine **282** was isolated as a stable compound. The structural identity of 3-pyrrolines **271** was further ascertained *via*

oxidation to the corresponding pyrroles **291** and bromination of the double bond present in 3-pyrroline (R_S)-**271a**.

4 Perspectives

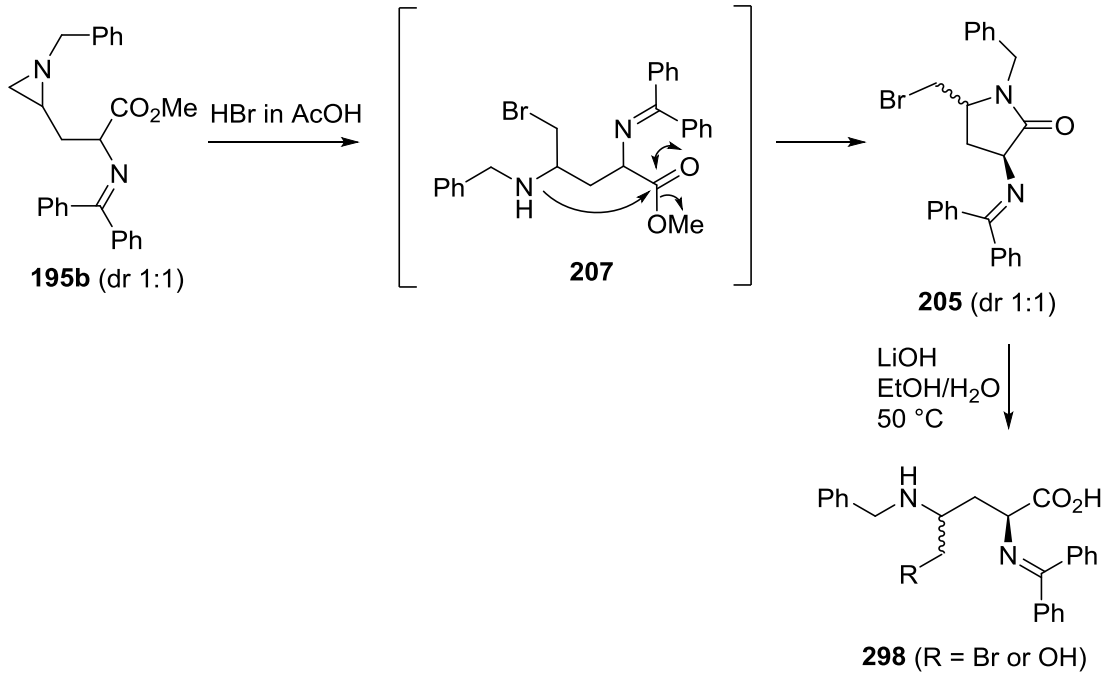
Within this PhD-thesis, the efficient synthesis of γ,δ-aziridino α-amino acid derivative **195b** was demonstrated. This compound proved to be a useful building block for the synthesis of different carbocyclic and heterocyclic compounds, including functionalized cyclopropanes, γ-lactams and γ-lactones. In view of the broad applicability of these synthons, the possibilities for further elaboration towards new heterocyclic compounds should be further exploited. For example, aziridine **195b** might be transformed into the corresponding oxazolidin-2-one **295** upon reaction with methyl chloroformate, as has been reported in literature for related aziridines (Scheme 86).[120] Recently, a new class of foldamers containing a 4-carboxyoxazolidin-2-one moiety was reported as new supramolecular materials.[121] In analogy, compound **295** might be incorporated in peptides to create new materials with interesting opportunities.



Scheme 86

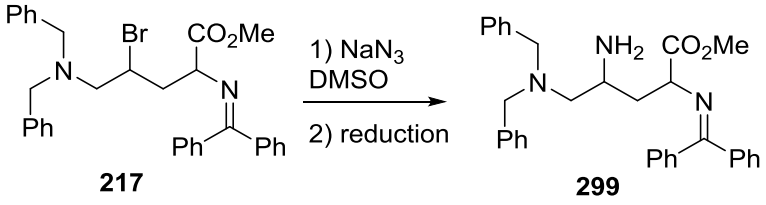
Treatment of aziridine **195b** with HBr resulted in the formation of the desired α,γ-diamino acid derivative **207**, which underwent ring closure to the corresponding lactams **205**. The observed ring closure might form a common problem with respect to the formation of the desired ring opening products and therefore it should be further investigated if this cyclization reaction can be avoided. Indeed, the presence of the bromine atom in amino acid derivative **207** makes it an interesting intermediate for further functionalization towards ring opening products with potentially interesting activities. Because of steric reasons, the introduction of a benzyl or *tert*-butyl ester instead of the

methyl ester might be a solution to avoid this cyclization. If not the case, it should be investigated if the resulting lactams are susceptible towards ring opening, which again would result in the formation of the desired α,γ-diamino acid derivatives. Indeed, related lactams have been successfully ring opened using LiOH and the same conditions could be used in an attempt to open lactam **205** to the corresponding α,γ-diamino acid **298** (Scheme 87).[45]



Scheme 87

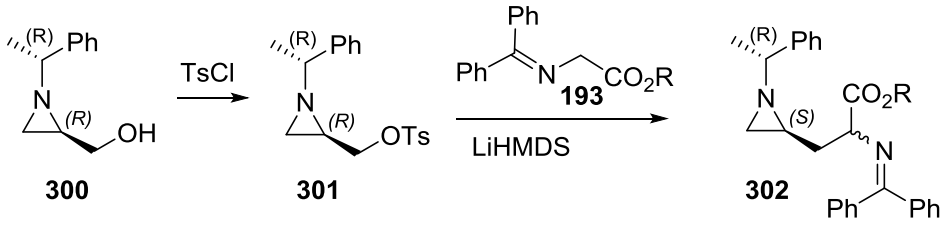
As mentioned before, reaction with benzyl bromide resulted in ring opening at the more substituted carbon atom of aziridine **195b** and β-bromo amine **217** could be isolated as a pure compound. Further functionalisation of this compound might also be investigated. For example, treatment with NaN_3, followed by reduction of the azide functionality would lead to α,γ,δ-triamino acid derivatives **299** as an interesting class of compounds (Scheme 88).



Scheme 88

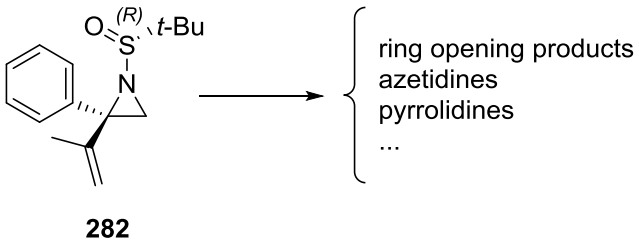
Due to the increasing interest in the development of new chiral amino acid derivatives, the asymmetric synthesis of the obtained γ-δ aziridino α-amino acid derivatives would be a valuable addition. Starting from the commercially available chiral aziridino alcohol **300**, it should be

investigated if transformation of the alcohol function into a good leaving group, followed by substitution with protected glycine derivatives **193** would lead to 2-(carboxyethyl)aziridines **302** as a mixture of diastereomers of which the separability should be further investigated (Scheme 89). If separation is not possible, the stereoselective ring transformation described in section 3.1.5 would still lead to the corresponding enantiomerically pure cyclopropanes.



Scheme 89

A second goal of this thesis was to synthesize chiral *N*-(*tert*-butanesulfinyl)-2-alkenylaziridines *via* addition of alkenylmagnesium bromides across aromatic *N*-sulfinyl α-chloroketimines. In the case of vinylmagnesium bromide, the resulting aziridines spontaneously rearranged to the corresponding 3-pyrrolines. When isopropenylmagnesium bromide was used however, 2-isopropenylaziridine **282** was isolated as a stable compound. Having this functionalized aziridine in hand, the potential of this compound as synthetic building block should be further evaluated (Scheme 90). Indeed, vinylaziridines were shown to be versatile intermediates for the synthesis of a variety of nitrogen-containing molecules *via* a range of transformations, including stereoselective nucleophilic ring opening reactions, as well as rearrangement and cycloaddition reactions.[24]



Scheme 90

5 Experimental part

5.1 General methods

Flame-dried glassware was used for all non-aqueous reactions. Commercially available solvents and reagents were purchased from common chemical suppliers and used without further purification, unless stated otherwise. The enantiopure reagents (R_S)- and (S_S)-*tert*-butanesulfinamide were commercially available (ee > 98%).

Tetrahydrofuran (THF) and diethyl ether (Et_2O) were freshly distilled under a nitrogen atmosphere from sodium and sodium/benzophenone ketyl prior to use, whereas dichloromethane (CH_2Cl_2) was distilled from calcium hydride. Petroleum ether refers to the 40-60 °C boiling fraction.

The purification of the reaction mixtures was performed by column chromatography with silica gel (Acros, particle size 0.035-0.070 mm, pore diameter ca. 6 nm). Thin layer chromatography (TLC) was performed on glass plates coated with silica gel (Merck, Kieselgel 60 F254, precoated 0.25 mm) using standard visualization techniques or agents: UV fluorescence (254 nm and 366 nm), coloring with iodine vapors or with potassium permanganate solution.

High resolution ^{1}H NMR (200 MHz, 300 MHz or 400 MHz), ^{13}C NMR (50 MHz, 75 MHz or 100 MHz) spectra were recorded with a Bruker AC 200 spectrometer, a Jeol Eclipse FT 300 NMR spectrometer or a Bruker Avance III Nanobay 400 MHz at room temperature unless specified otherwise. Peak assignments were obtained with the aid of DEPT, COSY and/or HSQC spectra. The compounds were diluted in deuterated solvents, quoted in parts per million (ppm) with tetramethylsilane (TMS, δ= 0 ppm) as internal standard unless specified otherwise.

Infrared spectra were recorded on a Perkin Elmer Spectrum BX FT-IR Spectrometer. All compounds were analyzed in neat form with an ATR (Attenuated Total Reflectance) accessory. Only selected absorbances (ν_{max}/cm^{-1}) were reported.

LC-MS analysis was performed with Agilent 1100 series SL (ES, 4000 V) equipment, preceded by a reverse phase LC-column (Eclipse plus C18 column). The LC column has dimensions of 50 x 4.6 mm and has a particle size of 3.5 µm. Gradient elution was used (30% acetonitrile in water to 100% acetonitrile over 6 minutes) and the MS analysis was performed *via* electron-spray ionization at 4 kV (positive mode) or 3.5 kV (negative mode) and fragmentation at 70 eV, with only molecular ions ($M + H^+$) and major peaks being reported with intensities quoted as percentage of the base peak, using either an LC-MS coupling or a direct inlet system.

High resolution mass spectra were obtained using an Agilent 1100 series HPLC coupled to an Agilent 6210 TOF-Mass Spectrometer, equipped with ESI/APCI-multimode source.

Elementary analyses were obtained by means of a Perkin Elmer series II CHNS/O elementary analyzer 2400.

Melting points of crystalline compounds were determined using a Büchi B-540 apparatus or a Kofler bench, type WME Heizbank of Wagner & Munz.

Optical rotations were determined using a JASCO P-2000 Series Polarimeter at a wavelength of 589 nm.

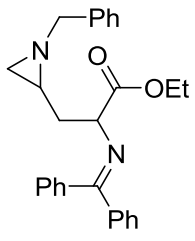
5.2 Synthesis of alkyl 3-(1-benzylaziridin-2-yl)-2-(diphenylmethyleneamino)-propanoates 195

The synthesis of ethyl 3-(1-benzylaziridin-2-yl)-2-(diphenylmethyleneamino)propanoate **195a** is representative. In a flame-dried round-bottomed flask, *N*-(diphenylmethylene)glycine ethyl ester **193a** (2.0 equiv, 2.00 mmol, 0.53 g) was dissolved in dry THF (5 mL) under nitrogen atmosphere. The solution was cooled to -78 °C, after which a 1M solution of LiHMDS (2.0 equiv, 2.00 mL, 2.00 mmol) in THF was added slowly and the mixture was allowed to stir for 1 hour. After this enolate formation, a solution of 1-benzyl-2-(bromomethyl)aziridine **194** (1.0 equiv, 1.00 mmol, 0.23 g) in dry THF (5 mL) was added dropwise. The reaction mixture was stirred for another hour at -78 °C, followed by 16 hours at reflux. The reaction mixture was brought to room temperature, a saturated solution of aqueous NH_4Cl (5 mL) was added and the reaction mixture was extracted with EtOAc (3 x 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated in vacuo. The crude product was purified by column chromatography to yield 0.34 g (0.89 mmol) of ethyl 3-(1-benzylaziridin-2-yl)-2-(diphenylmethyleneamino)propanoate **195a** as a 1:1 mixture of diastereomers.

Ethyl 3-(1-benzylaziridin-2-yl)-2-(diphenylmethyleneamino)propanoate 195a.

Spectral data were obtained from a mixture of two diastereomers in a 1:1 ratio.

R_f = 0.24 (petroleum ether/ethyl acetate 65:35). Brown oil, yield 89%, dr 1:1. IR (cm^{-1}): ν_{max} 695, 731, 1622, 1733. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 (3H, t, *J* = 7.2 Hz, $C\underline{H}_3CH_2O_{isomer\ 1}$), 1.23 (3H, t, *J* = 7.2 Hz, $C\underline{H}_3CH_2O_{isomer\ 2}$), 1.31 (1H, d, *J* = 6.1 Hz, $C\underline{H}(H)_{azir,\ isomer\ 1}$), 1.35 (1H, d, *J* = 6.1 Hz, $C\underline{H}(H)_{azir,\ isomer\ 2}$), 1.53 (1H, d, *J* = 3.3 Hz, $CH(\underline{H})_{azir,\ isomer\ 1}$), 1.56-1.66 (3H, m, $CH(\underline{H})_{azir,\ isomer\ 2}$ and 2 x $CH_{azir,\ isomer\ 1\ and\ 2}$), 1.87-2.00 (2H, m, 2 x $CHC\underline{H}(H)_{isomer\ 1\ and\ 2}$), 2.07-2.24 (2H, m, 2 x $CHCH(\underline{H})_{isomer\ 1\ and\ 2}$), 3.09 (1H, d, *J* = 13.8



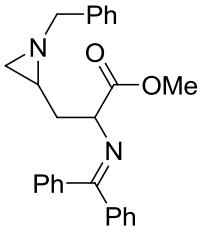
195a

Hz, NC<u>H</u>(H)Ph$_{isomer\ 1}$), 3.30 (1H, d, *J* = 13.2 Hz, NC<u>H</u>(H)Ph$_{isomer\ 2}$), 3.42 (1H, d, *J* = 13.2 Hz, NCH(<u>H</u>)Ph$_{isomer\ 2}$), 3.54 (1H, d, *J* = 13.8 Hz, NCH(<u>H</u>)Ph$_{isomer\ 1}$), 4.06-4.21 (5H, m, 2 x $CH_3C\underline{H}_2O_{isomer\ 1\ and\ 2}$ and C<u>H</u>$CO_2Et_{isomer\ 1}$), 4.32 (1H, dxd, *J* = 8.0 Hz, 4.7 Hz, C<u>H</u>$CO_2Et_{isomer\ 2}$), 7.14-7.69 (30H, m, 30 x $CH_{arom,\ isomer\ 1\ and\ 2}$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2 (2 x $\underline{C}H_3CH_2O_{isomer\ 1\ and\ 2}$), 34.0 and 34.3 (2 x $CH_{2,\ azir,\ isomer\ 1\ and\ 2}$), 36.7 and 36.8 (2 x $CH_{azir,\ isomer\ 1\ and\ 2}$), 37.4 (2 x CH$\underline{C}H_{2,\ isomer\ 1\ and\ 2}$), 60.9 and 61.0 (2 x $CH_3CH_2O_{isomer\ 1\ and\ 2}$), 64.17 and 64.24 (2 x $\underline{C}HCO_2Et_{isomer\ 1\ and\ 2}$), 64.65 and 64.73 (2 x $NCH_2Ph_{isomer\ 1\ and\ 2}$), 126.96, 127.04, 127.9, 128.0, 128.08, 128.14, 128.35, 128.40, 128.6, 128.7, 128.8, 128.9 and 130.4 (30 x $CH_{arom,\ isomer\ 1\ and\ 2}$), 136.5, 139.3, 139.65 and 139.70 (6 x $C_{arom,\ isomer\ 1\ and\ 2}$), 170.4 and 170.7 (2 x $C{=}N_{isomer\ 1\ and\ 2}$), 171.9, 172.1 (2 x $C{=}O_{isomer\ 1\ and\ 2}$). MS (ES, pos. mode) *m/z* (%): 413 (M + H^+, 100). HRMS (ES) calcd for $C_{27}H_{29}N_2O_2^+$: 413.2224 MH^+; found: 413.2219.

Methyl 3-(1-benzylaziridin-2-yl)-2-(diphenylmethyleneamino)propanoate 195b.

Spectral data were obtained from a mixture of two diastereomers in a 1:1 ratio.

R_f = 0.31 (petroleum ether/ethyl acetate 65:35). Brown oil, yield 70%, dr 1:1. IR (cm^{-1}): ν_{max} 695, 732, 1622, 1737. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31 (1H, d, *J* = 6.6 Hz, C<u>H</u>(H)$_{azir,\ isomer\ 1}$), 1.33 (1H, d, *J* = 6.6 Hz, C<u>H</u>(H)$_{azir,\ isomer\ 2}$), 1.51 (1H, d, *J* = 3.3 Hz, CH(<u>H</u>)$_{azir,\ isomer\ 1}$), 1.53-1.67 (3H, m, CH(<u>H</u>)$_{azir,\ isomer\ 2}$ and 2 x $CH_{azir,\ isomer\ 1\ and\ 2}$), 1.88-2.24 (4H, m, 2 x CHC<u>H</u>$_{2,\ isomer\ 1\ and\ 2}$), 3.05 (1H, d, *J* = 13.2 Hz, NC<u>H</u>(H)Ph$_{isomer\ 1}$), 3.27 (1H, d, *J* = 13.2 Hz, NC<u>H</u>(H)Ph$_{isomer\ 2}$), 3.42 (1H, d, *J* = 13.2 Hz, NCH(<u>H</u>)Ph$_{isomer\ 2}$), 3.53 (1H, d, *J* = 13.2 Hz, NCH(<u>H</u>)Ph$_{isomer\ 1}$), 3.63 and 3.67 (2 x 3H, 2 x s, 2 x $CH_3O_{isomer\ 1\ and\ 2}$), 4.18 (1H, dxd, *J* = 6.3 Hz, 6.3 Hz, C<u>H</u>$CO_2Me_{isomer\ 1}$), 4.30 (1H, dxd, *J* = 8.0 Hz, 4.7 Hz, C<u>H</u>$CO_2Me_{isomer\ 2}$), 7.14-7.48 (26H, m, 26 x $CH_{arom,\ isomer\ 1\ and\ 2}$), 7.63-7.67 (4H, m, 4 x $CH_{arom,\ isomer\ 1\ and\ 2}$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 33.8 and 34.0 (2 x $CH_{2,\ azir,\ isomer\ 1\ and\ 2}$), 36.4 and 36.6 (2 x $CH_{azir,\ isomer\ 1\ and\ 2}$), 37.37 and 37.40 (2 x CH$\underline{C}H_{2,\ isomer\ 1\ and\ 2}$), 51.95 and 52.04 (2 x $CH_3O_{isomer\ 1\ and\ 2}$), 64.0 (2 x $\underline{C}HCO_2Me_{isomer\ 1\ and\ 2}$), 64.5 and 64.6 (2 x $NCH_2Ph_{isomer\ 1\ and\ 2}$), 126.8, 126.9, 127.7, 127.8, 127.91, 127.97, 128.05, 128.2, 128.3, 128.6, 128.7, 128.8 and 130.4 (30 x $CH_{arom,\ isomer\ 1\ and\ 2}$), 136.2, 139.2, 139.4 and 139.5 (6 x $C_{arom,\ isomer\ 1\ and\ 2}$), 170.3 and 170.6 (2 x $C{=}N_{isomer\ 1\ and\ 2}$), 172.3 and 172.4 (2 x $C{=}O_{isomer\ 1\ and\ 2}$). MS (ES, pos. mode) *m/z* (%): 399 (M + H^+, 100). HRMS (ES) calcd for $C_{26}H_{27}N_2O_2^+$: 399.2067 MH^+; found: 399.2075.



195b

5.3 Synthesis of methyl 2-amino-3-(1-benzylaziridin-2-yl)propanoate 200

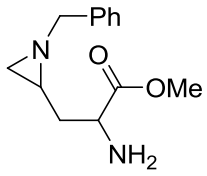
Methyl 3-(1-benzylaziridin-2-yl)-2-(diphenylmethyleneamino)propanoate **195b** (0.38 g, 0.95 mmol) was dissolved in a 2:1 mixture of acetone/water (6 mL), and trifluoroacetic acid (5 equiv, 4.77 mmol, 0.37 mL) was added dropwise at room temperature. The reaction mixture was stirred for 15 minutes at room temperature after which an aqueous solution of NH_4OH was added until a pH = 10 of the

solution was obtained. Acetone was evaporated in vacuo and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated in vacuo. The crude product was purified by column chromatography to yield 0.12 g (0.51 mmol) of methyl 2-amino-3-(1-benzylaziridin-2-yl)propanoate **200** as a 1:1 mixture of diastereomers.

Methyl 2-amino-3-(1-benzylaziridin-2-yl)propanoate 200.

Spectral data were obtained from a mixture of two diastereomers in a 1:1 ratio.

R_f = 0.25 (CH_2Cl_2/ MeOH 97:3). Yellow oil, yield 55%, dr 1:1. IR (cm^{-1}): ν_{max} 698, 734, 1170, 1201, 1733, 3366 (weak). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.43 (1H, d, *J* = 5.5 Hz, C<u>H</u>(H)$_{azir,\ isomer\ 1}$), 1.46-1.51 (1H, m, C<u>H</u>(H)$_{azir,\ isomer\ 2}$), 1.59-1.88 (8H, m, 2 x CH(<u>H</u>)$_{azir,\ isomer\ 1\ and\ 2}$, 2 x $CH_{azir,\ isomer\ 1\ and\ 2}$ and 2 x CHC<u>H</u>$_{2,\ isomer\ 1\ and\ 2}$), 1.89-1.95 (4H, br s, 2 x $NH_{2,\ isomer\ 1\ and\ 2}$), 3.29 (1H, d, *J* = 13.2 Hz, NC<u>H</u>(H)$Ph_{isomer\ 1}$), 3.32 (1H, d, *J* = 13.2 Hz, NC<u>H</u>(H)$Ph_{isomer\ 2}$), 3.49 (1H, d, *J* = 13.2 Hz, NCH(<u>H</u>)$Ph_{isomer\ 2}$), 3.52 (1H, d, *J* = 13.2 Hz, NCH(<u>H</u>)$Ph_{isomer\ 1}$), 3.39-3.56 (2H, m, 2 x C<u>H</u>$CO_2Me_{isomer\ 1\ and\ 2}$), 3.68 and 3.69 (2 x 3H, 2 x s, 2 x $CH_3O_{isomer\ 1\ and\ 2}$), 7.22-7.38 (10H, m, 10 x $CH_{arom,\ isomer\ 1\ and\ 2}$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 33.6 and 34.1 (2 x $CH_{2,\ azir,\ isomer\ 1\ and\ 2}$), 36.0 and 36.4 (2 x $CH_{azir,\ isomer\ 1\ and\ 2}$), 37.7 and 38.1 (2 x CH<u>C</u>$H_{2,\ isomer\ 1\ and\ 2}$), 51.9 (2 x $CH_3O_{isomer\ 1\ and\ 2}$), 53.2 and 53.4 (2 x <u>C</u>H$CO_2Me_{isomer\ 1\ and\ 2}$), 64.6 and 64.7 (2 x $NCH_2Ph_{isomer\ 1\ and\ 2}$), 127.15, 127.24, 128.2, 128.36 and 128.40 (10 x $CH_{arom,\ isomer\ 1\ and\ 2}$), 139.0 and 139.1 (2 x $C_{arom,\ isomer\ 1\ and\ 2}$), 175.9 and 176.0 (2 x $C{=}O_{isomer\ 1\ and\ 2}$). MS (ES, pos. mode) *m/z* (%): 235 (M + H^+, 100). HRMS (ES) calcd for $C_{13}H_{19}N_2O_2^+$: 235.1441 MH^+; found: 235.1448.



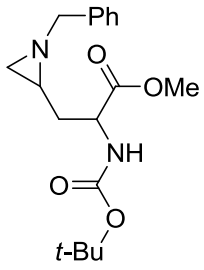
200

5.4 Synthesis of methyl 3-(1-benzylaziridin-2-yl)-2-*tert*-butoxycarbonylamino-propanoate 201

To a solution of methyl 2-amino-3-(1-benzylaziridin-2-yl)propanoate **200** (0.1 g, 0.43 mmol) in THF (5 mL) was added Et_3N (1.5 equiv, 0.65 mmol, 65 mg) and Boc_2O (1.5 equiv, 0.65 mmol, 140 mg). The reaction mixture was stirred for 16 hours at room temperature, water (5 mL) was added and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated in vacuo. The crude product was purified by column chromatography to yield 85 mg (0.25 mmol) of methyl 3-(1-benzylaziridin-2-yl)-2-*tert*-butoxycarbonylaminopropanoate **201** as a 1:1 mixture of diastereomers.

Methyl 3-(1-benzylaziridin-2-yl)-2-*tert*-butoxycarbonylaminopropanoate 201.

Spectral data were obtained from a mixture of two diastereomers in a 1:1 ratio.



201

R_f = 0.22 (petroleum ether/ethyl acetate 6:4). Yellow oil, yield 59%, dr 1:1. IR (cm^{-1}): ν_{max} 733, 1160, 1710, 1743, 3358 (weak). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38-1.42 (2H, m, 2 x C<u>H</u>(H)$_{azir,\ isomer\ 1\ and\ 2}$), 1.45 (2 x 9H, s, 2 x *t*-Bu$_{isomer\ 1\ and\ 2}$), 1.52-1.74 (6H, m, 2 x CH(<u>H</u>)$_{azir,\ isomer\ 1\ and\ 2}$, 2 x CH$_{azir,\ isomer\ 1\ and\ 2}$ and 2 x CHC<u>H</u>(H)$_{isomer\ 1\ and\ 2}$), 1.90-2.13 (2H, m, 2 x CHCH(<u>H</u>)$_{isomer\ 1\ and\ 2}$), 2.98 (1H, d, *J* = 13.2 Hz, NC<u>H</u>(H)Ph$_{isomer\ 1}$), 3.11 (1H, d, *J* = 13.2 Hz, NC<u>H</u>(H)Ph$_{isomer\ 2}$), 3.65-3.81 (2H, m, 2 x NCH(<u>H</u>)$_{isomer\ 1\ and\ 2}$), 3.71 and 3.72 (2x 3H, 2 x s, 2 x $CH_3O_{isomer\ 1\ and\ 2}$), 4.32-4.44 (2H, m, 2 x C<u>H</u>$CO_2Me_{isomer\ 1\ and\ 2}$), 5.61 (1H, br d, *J* = 7.2 Hz, NH$_{isomer\ 1}$), 5.71 (1H, br d, *J* = 7.7 Hz, NH$_{isomer\ 2}$), 7.21-7.38 (10H, m, 10 x CH$_{arom,\ isomer\ 1\ and\ 2}$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.3 (2 x (<u>C</u>$H_3)_3C_{isomer\ 1\ and\ 2}$), 33.3 and 33.6 (2 x $CH_{2,\ azir,\ isomer\ 1\ and\ 2}$), 34.9 and 35.3 (2 x CH$_{azir,\ isomer\ 1\ and\ 2}$), 35.6 and 35.8 (2 x CH<u>C</u>$H_{2,\ isomer\ 1\ and\ 2}$), 52.17 and 52.25 (2 x $CH_3O_{isomer\ 1\ and\ 2}$), 52.8 (2 x <u>C</u>H$CO_2Me_{isomer\ 1\ and\ 2}$), 64.3 and 64.4 (2 x $NCH_2Ph_{isomer\ 1\ and\ 2}$), 79.6 and 79.7 (2 x $(CH_3)_3$<u>C</u>$_{isomer\ 1\ and\ 2}$), 127.1, 127.2, 128.1, 128.3, 128.37 and 128.43 (10 x CH$_{arom,\ isomer\ 1\ and\ 2}$), 138.8 and 138.9 (2 x C$_{arom,\ isomer\ 1\ and\ 2}$), 155.4 (2 x NHC=O$_{isomer\ 1\ and\ 2}$), 172.8 and 172.9 (2 x C=O$_{isomer\ 1\ and\ 2}$). MS (ES, pos. mode) *m/z* (%): 335 (M + H^+, 15), 279 (M + H^+ - isobutene, 100). HRMS (ES) calcd for $C_{18}H_{27}N_2O_4^+$: 335.1965 MH^+; found: 335.1959 (15%), 279.1343 (100%).

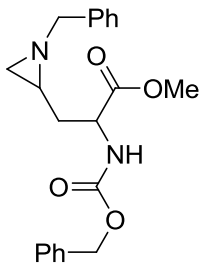
5.5 Synthesis of methyl 3-(1-benzylaziridin-2-yl)-2-benzyloxycarbonylamino-propanoate 202

To a solution of methyl 2-amino-3-(1-benzylaziridin-2-yl)propanoate **200** (0.18 g, 0.77 mmol) dissolved in a 1:1 mixture of dioxane/H_2O (5 mL) was added Et_3N (5 equiv, 3.85 mmol, 0.39 g). The solution was cooled to 0 °C and a solution of benzyl chloroformate (1.1 equiv, 0.85 mmol, 0.12 mL) in dioxane (2 mL) was added dropwise. After completion of the reaction (3 hours), the solvent was evaporated. Water was added and the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated in vacuo. The crude product was purified by column chromatography to yield 0.11 g (0.30 mmol) of methyl 3-(1-benzylaziridin-2-yl)-2-benzyloxycarbonylaminopropanoate **202** as a 1:1 mixture of two diastereomers.

Methyl 3-(1-benzylaziridin-2-yl)-2-benzyloxycarbonylaminopropanoate 202.

Spectral data were obtained from a mixture of two diastereomers in a 1:1 ratio.

R_f = 0.22 (petroleum ether/ethyl acetate 4:6). Yellow oil, yield 39%, dr 1:1. IR (cm^{-1}): ν_{max} 697, 729, 1212, 1717, 3332 (weak). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38 (1H, d, *J* = 3.3 Hz, C<u>H</u>(H)$_{azir,\ isomer\ 1}$), 1.40 (1H, d, *J* = 3.3 Hz, C<u>H</u>(H)$_{azir,\ isomer\ 2}$), 1.52-1.73 (6H, m, 2 x CH(<u>H</u>)$_{azir,\ isomer\ 1\ and\ 2}$, 2 x CH$_{azir,\ isomer\ 1\ and\ 2}$ and 2 x CHC<u>H</u>(H)$_{isomer\ 1\ and\ 2}$), 2.03-2.19 (2H, m, 2 x CHCH(<u>H</u>)$_{isomer\ 1\ and\ 2}$), 2.99 (1H, d, *J* = 13.2 Hz, NC<u>H</u>(H)$_{isomer\ 1}$),



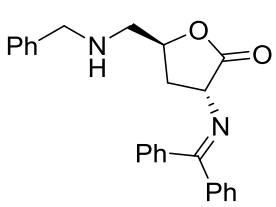
202

3.11 (1H, d, *J* = 13.2 Hz, NC<u>H</u>(H)$_{isomer\ 2}$), 3.59-3.81 (2H, m, 2 x NCH(<u>H</u>)$_{isomer\ 1\ and\ 2}$), 3.72 and 3.73 (2x 3H, 2 x s, 2 x $CH_3O_{isomer\ 1\ and\ 2}$), 4.39-4.48 (2H, m, 2 x C<u>H</u>$CO_2Me_{isomer\ 1\ and\ 2}$), 5.08-5.13 (4H, m, 2 x $CH_2O_{isomer\ 1\ and\ 2}$), 5.86 (1H, br d, *J* = 6.6 Hz, $NH_{isomer\ 1}$), 5.99 (1H, br d, *J* = 8.3 Hz, $NH_{isomer\ 2}$), 7.20-7.39 (20H, m, 20 x $CH_{arom,\ isomer\ 1\ and\ 2}$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 33.3 and 33.6 (2 x $CH_{2,\ azir,\ isomer\ 1\ and\ 2}$), 34.6 and 35.1 (2 x $CH_{azir,\ isomer\ 1\ and\ 2}$), 35.4 and 35.7(2 x C<u>H</u>$CH_{2,\ isomer\ 1\ and\ 2}$), 52.3 and 52.4 (2 x $CH_3O_{isomer\ 1\ and\ 2}$), 53.2 and 53.3 (2 x <u>C</u>H$CO_2Me_{isomer\ 1\ and\ 2}$), 64.4 (2 x $CH_2N_{isomer\ 1\ and\ 2}$), 66.8 and 66.9 (2 x $CH_2O_{isomer\ 1\ and\ 2}$), 127.1, 127.2, 128.07, 128.13, 128.3, 128.4 and 128.5 (20 x $CH_{arom,\ isomer\ 1\ and\ 2}$), 136.3, 136.5, 138.6 and 138.8 (4 x $C_{arom,\ isomer\ 1\ and\ 2}$), 155.8 and 155.9 (2 x NHC=$O_{isomer\ 1\ and\ 2}$), 172.5 and 172.6 (2 x C=$O_{isomer\ 1\ and\ 2}$). MS (ES, pos. mode) *m/z* (%): 369 (M + H^+, 100). HRMS (ES) calcd for $C_{21}H_{25}N_2O_4^+$: 369.1809 MH^+; found: 369.1813.

5.6 Synthesis of *cis*- and *trans*-4-[(benzylamino)methyl]-2-(diphenylmethyleneamino)butyrolactone (±)-199a and (±)-199b

Methyl 3-(1-benzylaziridin-2-yl)-2-(diphenylmethyleneamino)propanoate **195b** (110 mg, 0.28 mmol) was treated with 1M aqueous NaOH (5 equiv, 1.4 mmol, 1.4 mL) in a 3:1 mixture of MeOH/1M NaOH and the reaction mixture was allowed to stir for one hour at room temperature. The organic fraction was evaporated and ethyl acetate was added to the residue. The organic phase was dried ($MgSO_4$), filtered, and evaporated in vacuo. The crude product was purified by column chromatography to yield 74 mg (0.19 mmol) of 4-[(benzylamino)methyl]-2-(diphenylmethyleneamino)butyrolactone **199** as a 1:1 mixture of two diastereomers. Both diastereomers were separated from each other *via* preparative TLC to give *trans*- and *cis*-4-[(benzylamino)methyl]-2-(diphenylmethyleneamino)-butyrolactones (±)-**199a** and (±)-**199b** in 19% and 21% yield respectively.

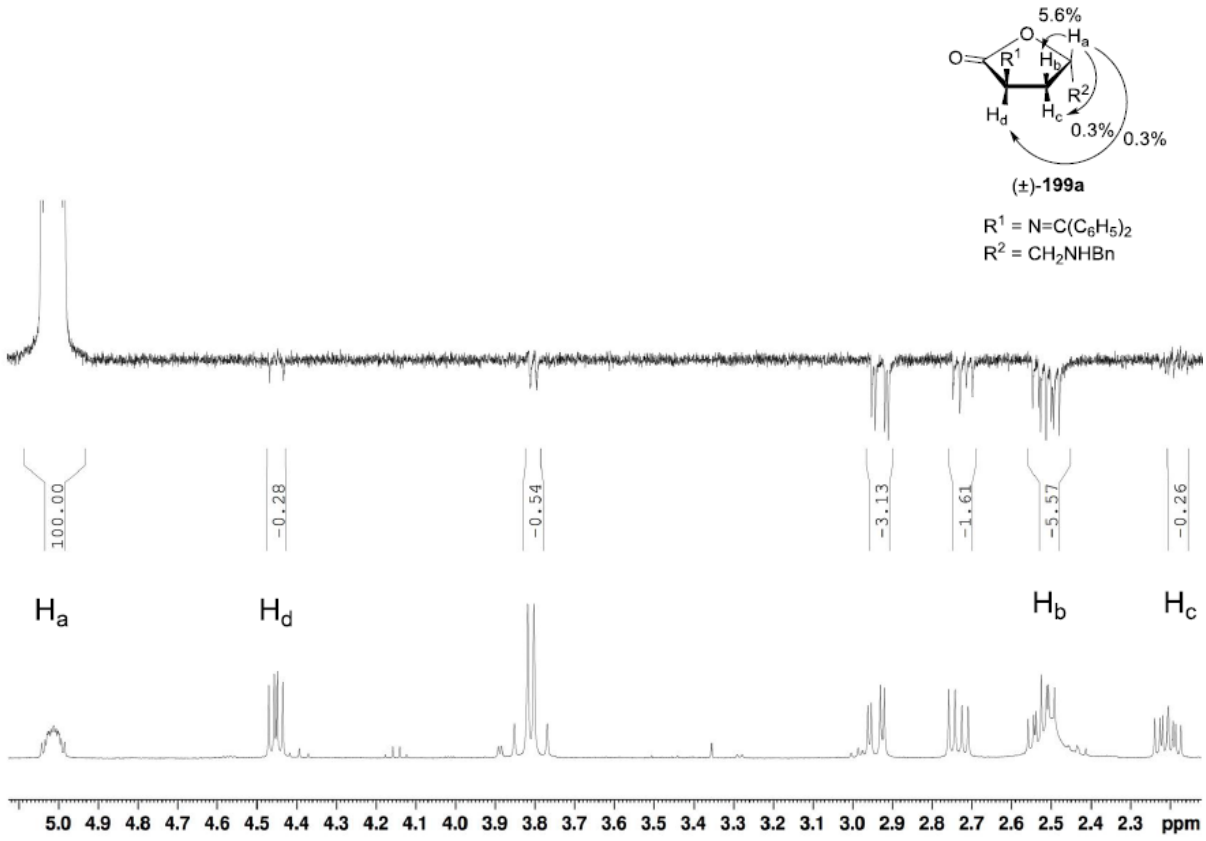
***Trans*-4-[(benzylamino)methyl]-2-(diphenylmethyleneamino)butyrolactone (±)-199a.** R_f = 0.2 (petroleum ether/EtOAc 1:1). Yellow oil, yield 19%. IR (cm^{-1}): ν_{max} 694, 1177, 1619, 1771. ^{1}H NMR



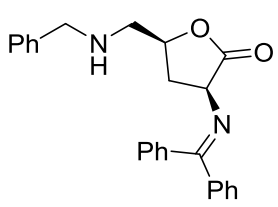
(±)-199a

(300 MHz, $CDCl_3$): δ 2.18 (1H, dxdxd, *J* = 13.0 Hz, 8.2 Hz, 5.5 Hz, C<u>H</u>(H)CHN), 2.50 (1H, dxdxd, *J* = 13.0 Hz, 7.6 Hz, 5.7 Hz, CH(<u>H</u>)CHN), 2.70 (1H, dxd, *J* = 13.0 Hz, 6.5 Hz, NHC<u>H</u>(H)CH), 2.91 (1H, dxd, *J* = 13.0 Hz, 3.5 Hz, NHCH(<u>H</u>)CH), 3.76 (1H, d, *J* = 13.3 Hz, NHC<u>H</u>(H)Ph), 3.80 (1H, d, *J* = 13.3 Hz, NHCH(<u>H</u>)Ph), 4.43 (1H, dxd, *J* = 8.2 Hz, 5.7 Hz, CHN), 4.95-5.02 (1H, m, CHO), 7.19-7.64 (15H, 15 x CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.7 (<u>C</u>H_2CHN), 52.6 (NH<u>C</u>H_2CH), 53.8 ($NHCH_2Ph$), 61.1 (CHN), 78.5 (CHO), 127.1, 128.1, 128.4, 128.5, 128.6, 129.0, 129.1 and 130.6 (15 x CH_{arom}), 135.6, 139.1 and 139.6 (3 x C_{arom}), 172.0 (C=N), 175.5 (C=O). MS (ES, pos. mode) *m/z* (%): 385 (M + H^+,100). HRMS (ES) calcd for $C_{25}H_{25}N_2O_2^+$: 385.1911 MH^+; found: 385.1929.

1D-NOESY of **(±)-199a**:

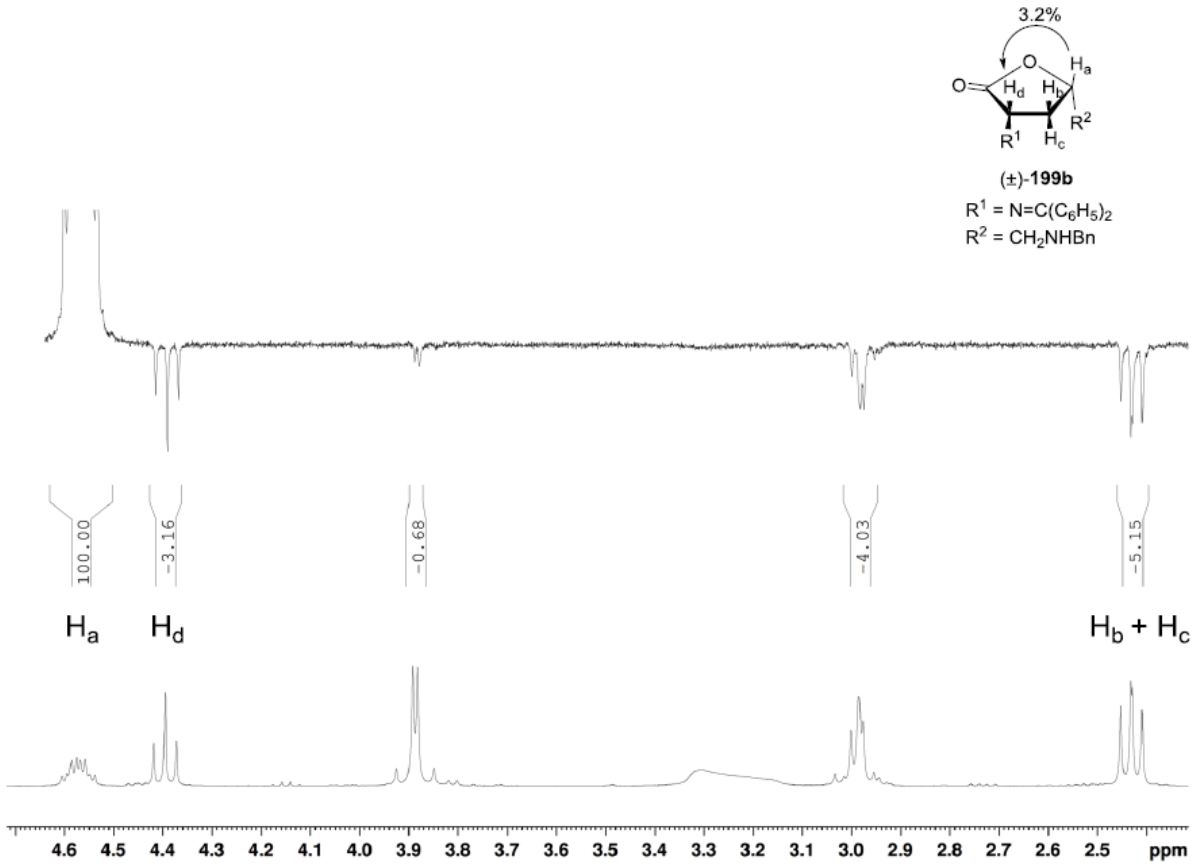


***Cis*-4-[(benzylamino)methyl]-2-(diphenylmethyleneamino)butyrolactone (±)-199b.** R_f = 0.11 (petroleum ether/EtOAc 1:1). Yellow oil, yield 21%. IR (cm^{-1}): ν_{max} 694, 1178, 1772. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.37-2.44 (2H, m, C<u>H</u>$_2$CHN), 2.89-3.02 (2H, m, NHC<u>H</u>$_2$CH), 3.83 (1H, d, *J* = 13.3 Hz, NHC<u>H</u>(H)Ph), 3.88 (1H, d, *J* = 13.3 Hz, NHCH(<u>H</u>)Ph), 4.36 (1H, dxd, *J* = 9.4 Hz, 9.4 Hz, CHN), 4.49-4.57 (1H, m, CHO), 7.23-7.64 (15H, m, 15 x CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 35.0 (<u>C</u>H$_2$CHN), 53.0 (NH<u>C</u>H$_2$CH), 53.7 ($NHCH_2Ph$), 61.5 (CHN), 78.5 (CHO), 127.1, 128.09, 128.13, 128.5, 128.6, 129.0, 129.1 and 130.7 (15 x CH_{arom}), 135.7, 139.0 and 139.6 (3 x C_{arom}), 172.9 (C=N), 174.8 (C=O). MS (ES, pos. mode) *m/z* (%): 385 (M + H^+,100). HRMS (ES) calcd for $C_{25}H_{25}N_2O_2^+$: 385.1911 MH^+; found: 385.1912.



(±)-199b

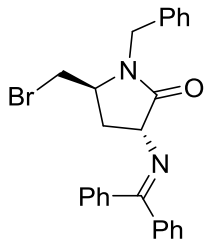
1D-NOESY of **(±)-199b**:



5.7 Synthesis of *cis*- and *trans*-1-benzyl-5-(bromomethyl)-3-(diphenylmethyleneamino)pyrrolidin-2-one (±)-205a and (±)-205b

To a solution of methyl 3-(1-benzylaziridin-2-yl)-2-(diphenylmethyleneamino)propanoate **195b** (1.5 g, 3.76 mmol) in CH_3CN (10 mL) was added a 33% hydrobromic acid solution in glacial acetic acid (2 equiv, 0.43 mL, 7.53 mmol) and the resulting mixture was stirred for 16 hours at room temperature. A saturated solution of $NaHCO_3$ (5 mL) was added and the reaction mixture was extracted with EtOAc (3 x 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated in vacuo. The crude mixture was dissolved in Et_2O and the obtained precipitate was filtered off to yield 0.69 g (1.54 mmol) of *trans*-1-benzyl-5-(bromomethyl)-3-(diphenylmethyleneamino)pyrrolidin-2-one (±)-**205a**, recrystallization of which from MeOH afforded crystals suitable for X-ray diffraction analysis. The filtrate was evaporated in vacuo and purified by column chromatography to yield 0.39 g (0.87 mmol) of *cis*-1-benzyl-5-(bromomethyl)-3-(diphenylmethyleneamino)pyrrolidin-2-one (±)-**205b**.

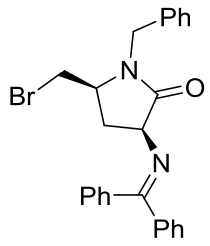
***Trans*-1-benzyl-5-(bromomethyl)-3-(diphenylmethyleneamino)pyrrolidin-2-one (±)-205a**. White crystals, yield 41%. Mp 150 ± 0.5 °C. IR (cm^{-1}): ν_{max} 699, 1249, 1429, 1682. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.14 (1H, dxdxd, *J* = 13.2 Hz, 8.3 Hz, 3.9 Hz, CHC<u>H</u>(H)CHN), 2.38 (1H, dxdxd, *J* = 13.2 Hz, 8.3 Hz, 6.1



(±)-**205a**

Hz, CHCH(H)CHN), 3.33-3.36 (2H, m, CH_2Br), 3.90-3.97 (1H, m, $CHCH_2Br$), 4.04 (1H, d, *J* = 15.4 Hz, NCH(H)Ph), 4.45 (1H, dxd, *J* = 8.3 Hz, 6.1 Hz, CHC=O), 5.03 (1H, d, *J* = 15.4 Hz, NCH(H)Ph), 7.25-7.50 (13H, m, CH_{arom}), 7.59-7.66 (2H, m, CH_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 33.0 ($CHCH_2CHN$), 34.7 (CH_2Br), 44.8 (NCH_2Ph), 55.0 ($CHCH_2Br$), 61.9 (CHC=O), 127.8, 127.9, 128.1, 128.4, 128.6, 128.8, 128.9 and 130.2 (15 x CH_{arom}), 135.7, 135.9 and 139.6 (3 x C_{arom}), 171.3 and 173.4 (C=N and C=O). MS (ES^+): *m/z* (%) = 447/449 ($M + H^+$, 100). HRMS (ES): calcd. for $C_{25}H_{24}{}^{79}BrN_2O^+$: 447.1067 MH^+; found 447.1077.

***Cis*-1-benzyl-5-(bromomethyl)-3-(diphenylmethyleneamino)pyrrolidin-2-one (±)-205b**. R_f = 0.31 (petroleum ether/ethyl acetate 8:2). Yellow oil, yield 23%. IR (cm^{-1}): ν_{max} 695, 1414, 1692. ^1H NMR



(±)-**205b**

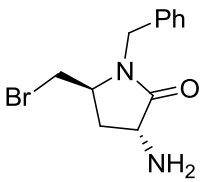
(300 MHz, $CDCl_3$): δ 2.15-2.33 (2H, m, $CHCH_2CHN$), 3.54-3.66 (3H, m, CH_2Br and $CHCH_2Br$), 4.18 (1H, d, *J* = 14.9 Hz, NCH(H)Ph), 4.26 (1H, dxd, *J* = 8.3 Hz, 5.5 Hz, CHC=O), 4.94 (1H, d, *J* = 14.9 Hz, NCH(H)Ph), 7.14-7.49 (13H, m, CH_{arom}), 7.58-7.65 (2H, m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 33.2 ($CHCH_2CHN$), 34.3 (CH_2Br), 45.0 (NCH_2Ph), 56.0 ($CHCH_2Br$), 62.3 (CHC=O), 127.7, 127.9, 128.0, 128.4, 128.6, 128.8, 128.9 and 130.3 (15 x CH_{arom}), 135.8, 136.2 and 139.4 (3 x C_{arom}), 170.9 and 173.3 (C=N and C=O). MS (ES^+): *m/z* (%) = 447/449 ($M + H^+$, 100). HRMS (ES): calcd. for $C_{25}H_{24}{}^{79}BrN_2O^+$: 447.1067 MH^+; found 447.1068.

5.8 Synthesis of *trans*-benzyl [1-benzyl-5-(bromomethyl)-2-oxopyrrolidin-3-yl]carbamate (±)-215

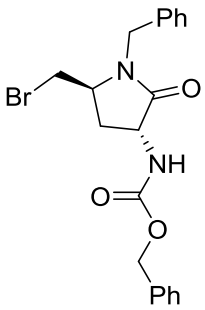
Trans-1-benzyl-5-(bromomethyl)-3-(diphenylmethyleneamino)pyrrolidin-2-one (±)-**205a** (44 mg, 0.98 mmol) was dissolved in a 2:1 mixture of acetone/water (6 mL) and trifluoroacetic acid (5 equiv, 4.88 mmol, 0.38 mL) was added dropwise at room temperature. The reaction mixture was stirred for 15 minutes at room temperature after which an aqueous solution of NH_4OH (28-30% NH_3) was added until pH = 10 of the solution was obtained. Acetone was evaporated in vacuo and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated in vacuo. The crude reaction mixture was used without any purification and dissolved in a 1:1 mixture of an aqueous saturated $NaHCO_3$ solution and Et_2O. The solution was cooled to 0 °C and benzyl chloroformate (1.01 equiv, 0.99 mmol, 0.14 mL) was added dropwise. The reaction mixture was allowed to stir for 15 minutes at 0 °C. The aqueous phase was extracted with Et_2O and the combined organic phases were dried ($MgSO_4$), filtered, and evaporated in vacuo. The crude product was purified by column chromatography to yield 240 mg (0.58 mmol) of *trans*-benzyl [1-benzyl-5-(bromomethyl)-2-oxopyrrolidin-3-yl]carbamate (±)-**215**.

The intermediate deprotected compound *trans*-3-amino-1-benzyl-5-(bromomethyl)pyrrolidin-2-one was purified once *via* column chromatography to allow full characterization of the compound.

***Trans*-3-amino-1-benzyl-5-(bromomethyl)pyrrolidin-2-one**. R_f = 0.19 (CH_2Cl_2/MeOH 95:5). Yellow oil, yield 40%. IR (cm^{-1}): ν_{max} 702, 727, 1682, 3364. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.83-1.96 (1H, m, C<u>H</u>(H)CHNH$_2$), 2.04-2.16 (2H, br s, NH$_2$), 2.40 (1H, dxdxd, *J* = 13.2 Hz, 8.8 Hz, 1.7 Hz, CH(<u>H</u>)CHNH$_2$), 3.34-3.45 (2H, m, CH$_2$Br), 3.70-3.79 (1H, m, C<u>H</u>CH$_2$Br), 3.89 (1H, dxd, *J* = 8.5 Hz, 8.5 Hz, CH$_2$C<u>H</u>NH$_2$), 4.04 (1H, d, *J* = 15.2 Hz, NC<u>H</u>(H)Ph), 4.96 (1H, d, *J* = 15.2 Hz, NCH(<u>H</u>)Ph), 7.22-7.39 (5H, m, CH$_{arom}$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 33.6 (<u>C</u>H$_2$CHNH$_2$), 34.3 (CH$_2$Br), 44.9 (NCH$_2$Ph), 51.5 (CH$_2$<u>C</u>HNH$_2$), 54.5 (<u>C</u>HCH$_2$Br), 128.0 (CH$_{arom}$), 128.1 (2 x CH$_{arom}$), 128.9 (2 x CH$_{arom}$), 135.6 (C$_{arom}$), 176.1 (C=O). MS (ES$^+$): *m/z* (%) = 283/285 (M + H$^+$, 100). HRMS (ES): calcd. for $C_{12}H_{16}{}^{79}BrN_2O_3^+$: 283.0441 MH$^+$; found 283.0450.



***Trans*-benzyl [1-benzyl-5-(bromomethyl)-2-oxopyrrolidin-3-yl]carbamate (±)-215**. R_f = 0.21 (petroleum ether/ethyl acetate 7:3). White crystals, yield 58%. Mp 98 ± 0.5 °C. IR (cm^{-1}): ν_{max} 697, 1246, 1684, 3304. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.07-2.18 (1H, m, C<u>H</u>(H)CHNH), 2.51-2.62 (1H, m, CH(<u>H</u>)CHNH), 3.34-3.45 (2H, m, CH$_2$Br), 3.75-3.82 (1H, m, C<u>H</u>CH$_2$Br), 4.05 (1H, d, *J* = 15.2 Hz, NC<u>H</u>(H)Ph), 4.48 (1H, dxt, *J* = 9.2 Hz, 5.6 Hz, CH$_2$C<u>H</u>NH), 5.01 (1H, d, *J* = 15.2 Hz, NCH(<u>H</u>)Ph), 5.12 (2H, s, OCH$_2$Ph), 5.47 (1H, br s, NH), 7.24-7.38 (10H, m, CH$_{arom}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.6 (<u>C</u>H$_2$CHNH), 34.4 (CH$_2$Br), 44.9 (NCH$_2$Ph), 51.4 (CH$_2$<u>C</u>HNH), 54.6 (<u>C</u>HCH$_2$Br), 66.8 (OCH$_2$Ph), 127.9, 127.97, 128.01, 128.4 and 128.8 (10 x CH$_{arom}$), 135.2 and 136.3 (2 x C$_{arom}$), 156.2 (NHC=O), 172.6 (C=O). MS (ES$^+$): *m/z* (%) = 417/419 (M + H$^+$, 100). HRMS (ES): calcd. for $C_{20}H_{22}{}^{79}BrN_2O_3^+$: 417.0808 MH$^+$; found 417.0828.



(±)-**215**

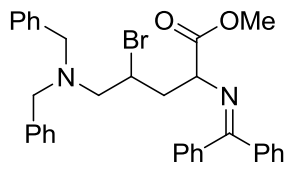
5.9 Synthesis of methyl 4-bromo-5-(dibenzylamino)-2-(diphenylmethylene-amino)pentanoate 217

To a solution of methyl 3-(1-benzylaziridin-2-yl)-2-(diphenylmethyleneamino)propanoate **195b** (0.3 g, 0.75 mmol) in CH_3CN (5 mL) was added benzyl bromide (2 equiv, 1.5 mmol, 0.26 g) and NaI (2 equiv, 1.5 mmol, 0.23 g). The reaction mixture was stirred for 3 hours at room temperature. After completion, the solids were filtered off and the solvent was evaporated in vacuo. The crude product was purified by column chromatography to yield 0.30 g (0.53 mmol) of methyl 4-bromo-5-(dibenzylamino)-2-(diphenylmethyleneamino)pentanoate **217** as a 1:1 mixture of diastereomers.

Methyl 4-bromo-5-(dibenzylamino)-2-(diphenylmethyleneamino)pentanoate 217.

Spectral data were obtained from a mixture of two diastereomers in a 1:1 ratio.

R_f = 0.27 (petroleum ether/ethyl acetate 9:1). Yellow oil, yield 82%, dr 1:1. IR (cm^{-1}): ν_{max} 695, 733, 1737. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.79 (1H, dxdxd, *J* = 14.7 Hz, 10.4 Hz, 4.4 Hz, C<u>H</u>(H)CHCO$_2$Me$_{isomer\ 1}$), 2.05 (1H, dxdxd, *J* = 14.5 Hz, *J* = 9.5 Hz, *J* = 2.5 Hz, C<u>H</u>(H)CHCO$_2$Me$_{isomer\ 2}$), 2.69-3.09 (6H, m, 2 x CH(<u>H</u>)CHCO$_2$Me$_{isomer\ 1\ and\ 2}$ and 2 x NC<u>H$_2$</u>CH$_{isomer\ 1\ and\ 2}$), 3.49 (2H, d, *J* = 13.2 Hz, 2 x NC<u>H</u>(H)Ph$_{isomer\ 1\ and\ 2}$), 3.51 (2H, d, *J* = 13.5 Hz, 2 x NC<u>H</u>(H)Ph$_{isomer\ 1\ and\ 2}$), 3.64 (2H, d, *J* = 13.2 Hz, 2 x NCH(<u>H</u>)Ph$_{isomer\ 1\ and\ 2}$), 3.67 (6H, s, 2 x CH$_3$O$_{isomer\ 1\ and\ 2}$), 3.72 (2H, d, *J* = 13.5 Hz, 2 x NCH(<u>H</u>)Ph$_{isomer\ 1\ and\ 2}$), 3.86-3.98 (1H, m, CHBr$_{isomer\ 1}$), 4.20-4.30 (1H, m, CHBr$_{isomer\ 2}$), 4.35 (1H, dxd, *J* = 10.4 Hz, 2.5 Hz, C<u>H</u>CO$_2$Me$_{isomer1}$), 4.42 (1H, dxd, *J* = 9.5 Hz, 4.4 Hz, C<u>H</u>CO$_2$Me$_{isomer2}$), 7.10-7.67 (40H, m, 40 x CH$_{arom,\ isomer\ 1\ and\ 2}$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 40.5 (2 x <u>C</u>H$_2$CHCO$_2$Me$_{isomer\ 1\ and\ 2}$), 50.3 (CHBr$_{isomer\ 1}$), 51.0 (CHBr$_{isomer\ 2}$), 52.2 (2 x CH$_3$O$_{isomer\ 1\ and\ 2}$), 58.5 (2 x N<u>C</u>H$_2$Ph$_{isomer\ 1\ and\ 2}$), 58.9 (2 x N<u>C</u>H$_2$Ph$_{isomer\ 1\ and\ 2}$), 61.1 (N<u>C</u>H$_2$CH$_{isomer\ 1}$), 61.2 (N<u>C</u>H$_2$CH$_{isomer\ 2}$), 62.9 (<u>C</u>HCO$_2$Me$_{isomer1}$), 63.9 (<u>C</u>HCO$_2$Me$_{isomer2}$), 127.06, 127.10, 127.3, 128.0, 128.1, 128.2, 128.3, 128.5, 128.72, 128.77, 128.86, 128.90, 129.1, 130.46 and 130.51 (40 x CH$_{arom,\ isomer\ 1\ and\ 2}$), 135.9, 136.1, 138.8, 139.3 and 139.4 (8 x C$_{arom,\ isomer\ 1\ and\ 2}$), 171.0, 172.2 and 172.4 (2 x C=N$_{isomer\ 1\ and\ 2}$ and 2 x C=O$_{isomer\ 1\ and\ 2}$). MS (ES, pos. mode) *m/z* (%): 569/571 (M + H^+, 25), 489 (M + H^+ - HBr, 100), 507 (M + H^+ - Br + OH, 9). HRMS (ES): calcd. for $C_{33}H_{34}{}^{79}BrN_2O_2^+$: 569.1798 MH^+; found 507.2646 (M + H^+ - Br + OH).



217

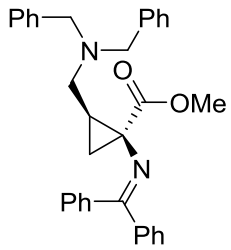
5.10 Synthesis of *cis*-methyl 2-[(dibenzylamino)methyl]-1-(diphenylmethyleneamino)cyclopropane-1-carboxylate (±)-*cis*-218

Procedure A: In a flame-dried round-bottomed flask, methyl 4-bromo-5-*N,N*-dibenzylamino-2-(diphenylmethyleneamino)pentanoate **217** (0.28 g, 0.49 mmol) was dissolved in dry THF (5 mL) under nitrogen atmosphere and the solution was cooled to -78 °C, after which a 1M solution of KHMDS (1.2 equiv, 0.59 mL, 0.59 mmol) in THF was added slowly and the mixture was allowed to stir for 2 hours at -78 °C. To the reaction mixture was added a saturated aqueous solution of NH_4Cl (5 mL) and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated in vacuo. The crude product was purified by flash chromatography, followed by recrystallization from ethanol to yield 0.17 g (0.35 mmol) of *cis*-methyl 2-[(dibenzylamino)methyl]-1-(diphenylmethyleneamino)cyclopropane-1-carboxylate (±)-*cis*-**218**.

Procedure B: A flame-dried round-bottomed flask was charged with methyl 4-bromo-5-*N,N*-dibenzylamino-2-(diphenylmethyleneamino)pentanoate **217** (0.25 g, 0.44 mmol) in dry CH_2Cl_2 (5 mL) under nitrogen atmosphere. The solution was cooled to 0 °C and DBU (1.2 equiv, 0.53 mmol, 0.08 g) was added. The mixture was stirred at room temperature for 1 hour. Water (5 mL) was added and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic phases were dried

($MgSO_4$), filtered, and evaporated in vacuo. The crude product was purified by flash chromatography, followed by recrystallization from ethanol to yield 0.14 g (0.29 mmol) of *cis*-methyl 2-[(dibenzylamino)methyl]-1-(diphenylmethyleneamino)cyclopropane-1-carboxylate (±)-*cis*-**218**.

***Cis*-methyl 2-[(dibenzylamino)methyl]-1-(diphenylmethyleneamino)cyclopropane-1-carboxylate (±)-*cis*-218.** R_f = 0.22 (petroleum ether/ethyl acetate 9:1). White crystals, yield 70% (Procedure A), 67% (Procedure B). Mp 98.5 ± 0.5 °C. IR (cm^{-1}): ν_{max} 696, 963, 1253, 1717. ^1H NMR (300 MHz, $CDCl_3$): δ 0.55 (1H, dxd, *J* = 7.2 Hz, 5.0 Hz, C<u>H</u>(H)$_{cycl}$), 1.56 (1H, dxd, *J* = 9.4 Hz, 5.0 Hz, CH(<u>H</u>)$_{cycl}$), 1.83-1.94 (1H, m, CH_{cycl}), 2.55 (1H, dxd, *J* = 13.2 Hz, 6.6 Hz, CHC<u>H</u>(H)N), 2.97 (1H, dxd, *J* = 13.2 Hz, 6.1 Hz, CHCH(<u>H</u>)N), 3.48 (3H, s, OCH_3), 3.57 (2H, d, *J* = 13.8 Hz, 2 x NC<u>H</u>(H)Ph), 3.81 (2H, d, *J* = 13.8 Hz, 2 x NCH(<u>H</u>)Ph), 7.06-7.52 (20H, m, 20 x CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.1 ($CH_{2,\ cycl}$), 28.5 (CH_{cycl}), 48.0 ($C_{q,\ cycl}$), 50.9 (CH<u>C</u>H_2N), 51.7 (OCH_3), 58.0 (2 x N<u>C</u>H_2Ph), 126.6, 127.8, 127.9, 128.0, 128.6, 128.7 and 130.3 (20 x CH_{arom}), 137.7, 139.78 and 139.83 (4 x C_{arom}), 172.7 and 173.9 (C=N and C=O). MS (ES, pos. mode) *m/z* (%): 489 (M + H^+, 100). HRMS (ES) calcd for $C_{33}H_{33}N_2O_2^+$: 489.2537 MH^+; found: 489.2539.

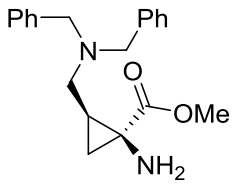


(±)-cis-**218**

5.11 Synthesis of *cis*-methyl 1-amino-2-[(dibenzylamino)methyl]cyclopropane-1-carboxylate (±)-220

Cis-methyl 2-[(dibenzylamino)methyl]-1-(diphenylmethyleneamino)cyclopropane-1-carboxylate (±)-*cis*-**218** (0.22 g, 0.45 mmol) was dissolved in a 2:1 mixture of acetone/water (6 mL), and trifluoroacetic acid (5 equiv, 2.25 mmol, 0.17 mL) was added dropwise at room temperature. The reaction mixture was stirred for 15 minutes at room temperature after which an aqueous solution of NH_4OH (28-30% NH_3) was added until pH = 10 of the solution was obtained. Acetone was evaporated in vacuo and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated in vacuo. The crude product was purified by column chromatography to yield 0.07 g (0.22 mmol) of *cis*-methyl 1-amino-2-[(dibenzylamino)methyl]-cyclopropane-1-carboxylate (±)-**220**.

***Cis*-methyl 1-amino-2-[(dibenzylamino)methyl]cyclopropane-1-carboxylate (±)-220.** R_f = 0.18 (petroleum ether/ethyl acetate 7:3). Yellow oil, yield 48%. IR (cm^{-1}): ν_{max} 698, 732, 1148, 1719, 3381 (weak). ^1H NMR (300 MHz, $CDCl_3$): δ 0.66 (1H, dxd, *J* = 7.2 Hz, 3.9 Hz, C<u>H</u>(H)$_{cycl}$), 1.43 (1H, dxd, *J* = 9.4 Hz, 3.9 Hz, CH(<u>H</u>)$_{cycl}$), 1.61-1.72 (3H, m, CH_{cycl} and NH_2), 2.67 (1H, dxd, *J* = 13.2 Hz, 5.5 Hz, CHC<u>H</u>(H)N), 2.75 (1H, dxd, *J* = 13.2 Hz, 7.2 Hz, CHCH(<u>H</u>)N), 3.55 (2H, d, *J* = 13.8 Hz, 2 x NC<u>H</u>(H)Ph), 3.63 (3H, s, OCH_3), 3.68 (2H, d, *J* = 13.8 Hz, 2 x NCH(<u>H</u>)Ph), 7.18-7.39 (10H, m, 10 x CH_{arom}).



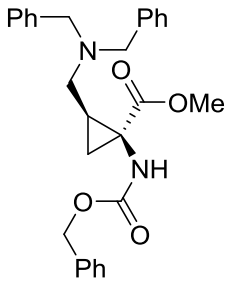
(±)-**220**

^{13}C NMR (75 MHz, $CDCl_3$): δ 23.0 ($CH_{2,\ cycl}$), 26.2 (CH_{cycl}), 38.9 ($C_{q,\ cycl}$), 52.2 (OCH_3), 52.5 (CH<u>C</u>H_2N), 58.6 (2 x N<u>C</u>H_2Ph), 126.9, 128.2 and 128.8 (10 x CH_{arom}), 139.8 (2 x C_{arom}), 176.7 (C=O). MS (ES, pos. mode) *m/z* (%): 325 (M + H^+, 100). HRMS (ES) calcd for $C_{20}H_{25}N_2O_2^+$: 325.1911 MH^+; found: 325.1918.

5.12 Synthesis of *cis*-methyl 1-(benzyloxycarbonylamino)-2-[(dibenzylamino)-methyl]cyclopropane-1-carboxylate (±)-221

Cis-methyl 1-amino-2-[(dibenzylamino)methyl]cyclopropane-1-carboxylate (±)-**220** (0.28 g, 0.86 mmol) was dissolved in a 1:1 mixture of an aqueous saturated $NaHCO_3$ solution and Et_2O. The solution was cooled to 0 °C and benzyl chloroformate (1.01 equiv, 0.87 mmol, 0.12 mL) was added dropwise. The reaction mixture was allowed to stir for 15 minutes at 0 °C. The aqueous phase was extracted with Et_2O and the combined organic phases were dried ($MgSO_4$), filtered, and evaporated in vacuo. The crude product was purified by column chromatography to yield 0.27 g (0.59 mmol) of *cis*-methyl 1-(benzyloxycarbonylamino)-2-[(dibenzylamino)methyl]cyclopropane-1-carboxylate (±)-**221**.

***Cis*-methyl 1-(benzyloxycarbonylamino)-2-[(dibenzylamino)methyl]cyclopropane-1-carboxylate (±)-221.** R_f = 0.14 (petroleum ether/ethyl acetate 4:1). Yellow oil, yield 69%. IR (cm^{-1}): ν_{max} 698, 728, 1722, 3378 (weak). ^{1}H NMR (300 MHz, $CDCl_3$, 50 °C): δ 0.85-0.99 (1H, m, C<u>H</u>(H)$_{cycl}$), 1.73-1.87 (2H, m, CH(<u>H</u>)$_{cycl}$ and CH_{cycl}), 2.39-2.52 (1H, m, CHC<u>H</u>(H)N), 2.70 (1H, dxd, *J* = 13.5 Hz, 5.2 Hz, CHCH(<u>H</u>)N), 3.36 (2H, d, *J* = 13.2 Hz, 2 x NC<u>H</u>(H)Ph), 3.61 (3H, s, OCH_3), 3.78 (2H, d, *J* = 13.2 Hz, 2 x NCH(<u>H</u>)Ph), 5.02 (1H, d, *J* = 12.4 Hz, OC<u>H</u>(H)Ph), 5.09 (1H, d, *J* = 12.4 Hz, OCH(<u>H</u>)Ph), 5.87 (1H, br s, NH), 7.12-7.39 (15H, m, 15 x CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.9 ($CH_{2,\ cycl}$), 25.3 (CH_{cycl}), 37.8 ($C_{q,\ cycl}$), 52.4 (OCH_3), 53.9 (CH<u>C</u>H_2N), 58.9 (2 x N<u>C</u>H_2Ph), 66.6 (O<u>C</u>H_2Ph), 127.2, 128.0, 128.1, 128.3, 128.4 and 128.8 (15 x CH_{arom}), 136.5 and 138.6 (3 x C_{arom}), 156.8 (NHC=O), 172.9 (C=O). MS (ES, pos. mode) *m/z* (%): 459 (M + H^+, 100). HRMS (ES) calcd for $C_{28}H_{31}N_2O_4^+$: 459.2278 MH^+; found: 459.2283.



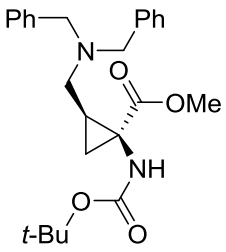
(±)-**221**

5.13 Synthesis of *cis*-methyl 1-(*tert*-butoxycarbonylamino)-2-[(dibenzylamino)-methyl]cyclopropane-1-carboxylate (±)-222

To a solution of *cis*-methyl 1-amino-2-[(dibenzylamino)methyl]cyclopropane-1-carboxylate (±)-**220** (0.2 g, 0.62 mmol) in THF (5 mL) was added Boc_2O (1.2 equiv, 0.74 mmol, 162 mg) and Et_3N (1.2 equiv, 0.74 mmol, 75 mg). The reaction mixture was stirred for 16 hours at room temperature, water (5 mL) was added and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated in vacuo. The crude product was

purified by column chromatography to yield 0.14 g (0.33 mmol) of *cis*-methyl 1-(*tert*-butoxycarbonylamino)-2-[(dibenzylamino)methyl]cyclopropane-1-carboxylate (±)-**222**.

***Cis*-methyl 1-(*tert*-butoxycarbonylamino)-2-[(dibenzylamino)methyl]cyclopropane-1-carboxylate (±)-222.** R_f = 0.18 (petroleum ether/ethyl acetate 4:1). Yellow oil, yield 53%. IR (cm^{-1}): ν_{max} 698, 734, 1159, 1720, 3358. ^1H NMR (300 MHz, $CDCl_3$): δ 1.23-1.28 (1H, m, C<u>H</u>(H)$_{cycl}$), 1.43 (9H, s, *t*-Bu), 1.33-1.85 (2H, m, CH(<u>H</u>)$_{cycl}$ and CH_{cycl}), 2.41-2.53 (1H, m, CHC<u>H</u>(H)N), 2.66 (1H, d, *J* = 12.1 Hz, CHCH(<u>H</u>)N), 3.37 (2H, d, *J* = 12.9 Hz, 2 x NC<u>H</u>(H)Ph), 3.63 (3H, s, OCH_3), 3.76 (2H, d, *J* = 12.9 Hz, 2 x NCH(<u>H</u>)Ph), 5.64 (1H, br s, NH), 7.17-7.39 (10H, m, 10 x CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.6 ($CH_{2,\ cycl}$), 25.2 (CH_{cycl}), 28.3 (C(<u>C</u>H_3)$_3$), 37.8 ($C_{q,\ cycl}$), 52.3 (OCH_3), 53.9 (CH<u>C</u>H_2N), 59.0 (2 x NCH_2Ph), 79.5 (<u>C</u>(CH_3)$_3$) , 127.1, 128.4 and 128.9 (10 x CH_{arom}), 138.9 (2 x C_{arom}), 156.3 (NHC=O), 173.2 (C=O). MS (ES, pos. mode) *m/z* (%): 425 (M + H^+, 100). HRMS (ES) calcd for $C_{25}H_{33}N_2O_4^+$: 425.2435 MH^+; found: 425.2440.

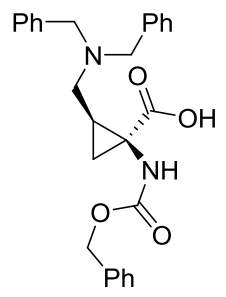


(±)-**222**

5.14 Synthesis of *cis*-1-(benzyloxycarbonylamino)-2-[(dibenzylamino)methyl]-cyclopropane-1-carboxylic acid (±)-223

Cis-methyl 1-(benzyloxycarbonylamino)-2-[(dibenzylamino)methyl]cyclopropane-1-carboxylate (±)-**221** (0.20 g, 0.44 mmol) was treated with 1M aq. NaOH (5 equiv, 2.2 mmol, 2.2 mL) in a 1:3 mixture of 1M NaOH/MeOH. The reaction mixture was stirred for 1 hour at reflux, after which MeOH was evaporated in vacuo. The aqueous phase was brought to pH = 4 with 1M aq. HCl and extracted with EtOAc (3 x 10 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated in vacuo. Precipitation in diethyl ether afforded 0.16 g (0.36 mmol) of *cis*-1-(benzyloxycarbonylamino)-2-[(dibenzylamino)methyl]cyclopropane-1-carboxylic acid (±)-**223**.

***Cis*-1-(benzyloxycarbonylamino)-2-[(dibenzylamino)methyl]cyclopropane-1-carboxylic acid (±)-223.** White amorphous solid, yield 81%. Mp 169.5 ± 0.5 °C. IR (cm^{-1}): ν_{max} 697, 740, 1236, 1726, 3218 (weak). ^1H NMR (300 MHz, CD_3OD): δ 0.98 (1H, dxd, *J* = 7.2 Hz, 5.5 Hz, C<u>H</u>(H)$_{cycl}$), 1.60 (1H, dxd, *J* = 9.4 Hz, 5.5 Hz, CH(<u>H</u>)$_{cycl}$), 2.13-2.26 (1H, m, CH_{cycl}), 3.12 (1H, dxd, *J* = 13.8 Hz, 8.8 Hz, CHC<u>H</u>(H)N), 3.36 (1H, dxd, *J* = 13.8 Hz, 6.1 Hz, CHCH(<u>H</u>)N), 4.19 (2H, d, *J* = 13.2 Hz, 2 x NC<u>H</u>(H)Ph), 4.29-4.47 (2H, m, 2 x NCH(<u>H</u>)Ph), 4.94 (1H, d, *J* = 12.7 Hz, OC<u>H</u>(H)Ph), 5.08 (1H, d, *J* = 12.7 Hz, OCH(<u>H</u>)Ph), 7.12-7.49 (15H, m, 15 x CH_{arom}). ^{13}C NMR (75 MHz, CD_3OD): δ 19.9 ($CH_{2,\ cycl}$), 21.6 (CH_{cycl}), 38.5 ($C_{q,\ cycl}$), 53.4 (CH<u>C</u>H_2N), 57.7 (2 x NCH_2Ph), 67.2



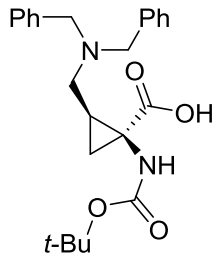
(±)-**223**

(O<u>C</u>H$_2$Ph), 127.4, 127.9, 128.3, 129.3, 129.5, 130.0 and 130.8 (15 x CH$_{arom}$), 136.3 (3 x C$_{arom}$), 160.1 (NHC=O), 172.7 (C=O). MS (ES, pos. mode) *m/z* (%): 445 (M + H$^+$, 100). HRMS (ES) calcd for $C_{27}H_{29}N_2O_4^+$: 445.2122 MH$^+$; found: 445.2120.

5.15 Synthesis of *cis*-1-(*tert*-butoxycarbonylamino)-2-[(dibenzylamino)methyl]-cyclopropane-1-carboxylic acid (±)-224

Cis-methyl 1-(*tert*-butoxycarbonylamino)-2-[(dibenzylamino)methyl]cyclopropane-1-carboxylate (±)-**222** (0.17 g, 0.40 mmol) was treated with 1M aq. NaOH (5 equiv, 2 mmol, 2 mL) in a 1:3 mixture of 1M NaOH/MeOH. The reaction mixture was stirred for 1 hour at room temperature, after which MeOH was evaporated in vacuo. The aqueous phase was brought to pH = 4 with 2M aq. HCl and extracted with EtOAc (3 x 10 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated in vacuo. Precipitation in diethyl ether afforded 0.10 g (0.24 mmol) of *cis*-1-(*tert*-butoxycarbonylamino)-2-[(dibenzylamino)methyl]cyclopropane-1-carboxylic acid (±)-**224**.

***Cis*-1-(*tert*-butoxycarbonylamino)-2-[(dibenzylamino)methyl]cyclopropane-1-carboxylic acid (±)-224.** White amorphous solid, yield 81%. Mp 135 ± 0.5 °C. IR (cm^{-1}): ν_{max} 698, 753, 1161, 1717, 1737, 3261 (weak). ^{1}H NMR (300 MHz, CD_3OD): δ 0.97 (1H, dxd, *J* = 6.6 Hz, 5.5 Hz, C<u>H</u>(H)$_{cycl}$), 1.37 (9H, s, *t*-Bu), 1.58 (1H, dxd, *J* = 8.8 Hz, 5.5 Hz, CH(<u>H</u>)$_{cycl}$), 2.03-2.15 (1H, m, CH$_{cycl}$), 3.15 (1H, dxd, *J* = 14.0 Hz, 7.2 Hz, CHC<u>H</u>(H)N), 3.28 (1H, dxd, *J* = 14.0 Hz, 7.7 Hz, CHCH(<u>H</u>)N), 4.25 (2H, d, *J* = 13.2 Hz, 2 x NC<u>H</u>(H)Ph), 4.38 (2H, d, *J* = 13.2 Hz, 2 x NCH(<u>H</u>)Ph), 7.34-7.49 (10H, m, 10 x CH$_{arom}$). ^{13}C NMR (75 MHz, CD_3OD): δ 20.4 (CH$_{2,\ cycl}$), 21.5 (CH$_{cycl}$), 27.4 (*t*-Bu), 53.4 (C$_{q,\ cycl}$), 57.5 (CH<u>C</u>H$_2$N), 65.6 (2 x NCH$_2$Ph), 80.6 (<u>C</u>(CH$_3$)$_3$), 129.2, 129.7, 129.9 and 130.7 (10 x CH$_{arom}$), 135.6 (3 x C$_{arom}$), 159.1 (NHC=O), 173.1 (C=O). MS (ES, pos. mode) *m/z* (%): 411 (M + H$^+$, 100). HRMS (ES) calcd for $C_{24}H_{31}N_2O_4^+$: 411.2278 MH$^+$; found: 411.2296.

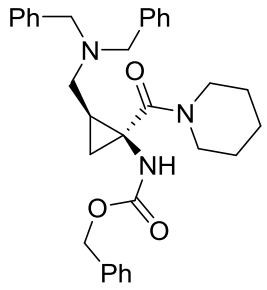


(±)-**224**

5.16 Synthesis of *cis*-benzyl {2-[(dibenzylamino)methyl]-1-(piperidine-1-carbonyl)cyclopropyl}carbamate (±)-225

A flame-dried round-bottomed flask was charged with *cis*-1-(benzyloxycarbonylamino)-2-[(dibenzylamino)methyl]cyclopropane-1-carboxylic acid (±)-**223** (300 mg, 0.67 mmol) in anhydrous CH_2Cl_2 (10 mL) under a nitrogen atmosphere. To the solution was added HOAt (1 equiv, 0.67 mmol, 93 mg) and EDC·HCl (1 equiv, 0.67 mmol, 128 mg) and the solution was stirred for 5 minutes at room temperature, after which piperidine (2 equiv, 1.34 mmol, 115 mg) and Et_3N (to pH 8) were added. The reaction mixture was stirred for 16 hours, the solvent was evaporated, and the crude product was purified by column chromatography to give 250 mg (0.49 mmol) of *cis*-benzyl {2-[(dibenzylamino)methyl]-1-(piperidine-1-carbonyl)cyclopropyl}carbamate (±)-**225**.

***Cis*-benzyl {2-[(dibenzylamino)methyl]-1-(piperidine-1-carbonyl)cyclopropyl}carbamate (±)-225.** R_f = 0.17 (petroleum ether/ethyl acetate 3:2). Yellow oil, yield 73%. IR (cm^{-1}): ν_{max} 697, 730, 1234, 1451, 1624, 1720, 3265 (weak). ^{1}H NMR (300 MHz, $CDCl_3$, 50 °C): δ 0.70-0.89 (1H, m, C<u>H</u>(H)$_{cycl}$), 1.36-1.77 (8H, m, CH(<u>H</u>)$_{cycl}$, CH_{cycl} and 3 x CH_2), 2.42 (1H, dxd, *J* = 13.2 Hz, 8.8 Hz, CHC<u>H</u>(H)N), 2.67 (1H, dxd, *J* = 13.2 Hz, 5.5 Hz, CHCH(<u>H</u>)N), 3.32 (2H, d, *J* = 13.2 Hz, 2 x NC<u>H</u>(H)Ph), 3.44-3.62 (4H, m, 2 x NCH_2), 3.95 (2H, d, *J* = 13.2 Hz, 2 x NCH(<u>H</u>)Ph), 4.89-5.01 (1H, m, OC<u>H</u>(H)Ph), 5.06 (1H, d, *J* = 12.1 Hz, OCH(<u>H</u>)Ph), 5.77 (1H, br s, NH), 7.13-7.38 (15H, m, 15 x CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.0 ($CH_{2,\ cycl}$), 21.4 (CH_{cycl}), 24.6 and 25.9 (3 x CH_2), 39.3 ($C_{q,\ cycl}$), 45.6 (2 x NCH_2), 53.2 (CH<u>C</u>H_2N), 58.3 (2 x NCH_2Ph), 66.6 (O<u>C</u>H_2Ph), 127.2, 128.1, 128.4, 128.5 and 128.9 (15 x CH_{arom}), 136.5 and 138.5 (3 x C_{arom}), 156.0 (NHC=O), 169.3 (C=O). MS (ES, pos. mode) *m/z* (%): 512 (M + H^+, 100). HRMS (ES) calcd for $C_{32}H_{38}N_3O_3^+$: 512.2908 MH^+; found: 512.2909.

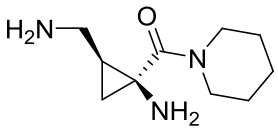


(±)-**225**

5.17 Synthesis of *cis*-[1-amino-2-(aminomethyl)cyclopropyl](piperidin-1-yl)-methanone (±)-219

To a solution of *cis*-benzyl {2-[(dibenzylamino)methyl]-1-(piperidine-1-carbonyl)cyclopropyl}-carbamate (±)-**225** (50 mg, 0.1 mmol) in MeOH (5 mL) was added Pd/C (20% mass fraction, 10 mg). The reaction mixture was stirred for four hours at room temperature under a H_2 atmosphere (1.8 bar) and subsequently filtered through a syringe filter. The organic phase was evaporated in vacuo to yield 18 mg (0.09 mmol) of *cis*-[1-amino-2-(aminomethyl)cyclopropyl](piperidin-1-yl)methanone (±)-**219** as a colorless oil.

***Cis*-[1-amino-2-(aminomethyl)cyclopropyl](piperidin-1-yl)methanone (±)-219.** Colorless oil, 91% yield. IR (cm^{-1}): ν_{max} = 1133, 1252, 1280, 1363, 1441, 1468, 1606, 2855, 2933, 3359. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* = 0.59 (1H, dxd, *J* = 6.6 Hz, 5.1 Hz, C<u>H</u>(H)$_{cycl}$), 1.16 (1H, dxd, *J* = 9.5 Hz, 5.1 Hz, CH(<u>H</u>)$_{cycl}$), 1.25–1.33 (1H, m, CH_{cycl}), 1.50–1.71 (6H, m, 3 x CH_2), 1.85-2.13 (4H, br s, 2 x NH_2), 2.91 (1H, dxd, *J* = 13.1 Hz, 7.5 Hz, C<u>H</u>(H)NH_2), 2.99 (1H, dxd, *J* = 13.1 Hz, 6.0 Hz, CH(<u>H</u>)NH_2), 3.52–3.65 (4H, m, 2 x NCH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): *δ* = 17.7 ($CH_{2,\ cycl}$), 24.6 (CH_2), 25.8 (CH_{cycl}), 25.9 (2 x NCH_2<u>C</u>H_2), 40.2 (CH_2NH_2), 40.3 ($C_{q,\ cycl}$), 44.9 (2 x NCH_2), 171.9 (C=O). MS (ES^+): *m/z* (%) = 198 (M + H^+, 100). HRMS (ES): calcd. for $C_{10}H_{20}N_3O^+$: 198.1601 MH^+; found 198.1602.



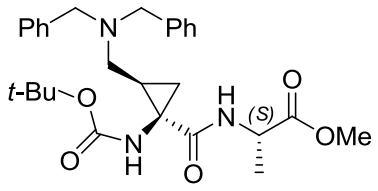
(±)-**219**

5.18 Synthesis of dipeptides 237, 238, (±)-243a, (±)-243b and 254

The synthesis of (*S*)-methyl 2-{1-(*tert*-butoxycarbonylamino)-2-[(dibenzylamino)methyl]-cyclopropanecarboxamido}propanoate **238** is representative. To a solution of *cis*-1-(*tert*-butoxycarbonyl amino)-2-[(dibenzylamino)methyl]cyclopropane-1-carboxylic acid (±)-**224** (50 mg, 0.12 mmol) in dry CH_2Cl_2 (5mL) was added HOAt (1 equiv, 0.12 mmol, 16 mg) and the resulting mixture was allowed to stir for five minutes at room temperature, after which EDC.HCl (1 equiv, 0.12 mmol, 23 mg) was added in one portion. Again the reaction mixture was stirred for five minutes, followed by the addition of (*S*)-alanine methyl ester hydrochloride **234** (2 equiv, 0.24 mmol, 34 mg) and Et_3N until a pH ≈ 8 of the solution was obtained. The reaction mixture was allowed to stir for 16 hours at room temperature and the solvent was evaporated in vacuo. The crude product was purified by column chromatography to yield 50 mg (0.10 mmol) of (*S*)-methyl 2-{1-(*tert*-butoxycarbonylamino)-2-[(dibenzylamino)methyl]cyclopropanecarboxamido}propanoate **238**.

(*S*)-Methyl 2-{1-(*tert*-butoxycarbonylamino)-2-[(dibenzylamino)methyl]cyclopropanecarboxamido}propanoate 238.

Spectral data were obtained from a mixture of two diastereomers in a 1:1 ratio.

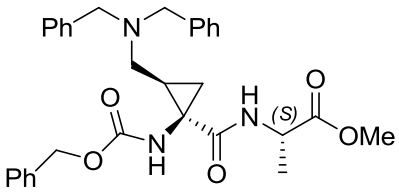


238

R_f = 0.23 (petroleum ether/ethyl acetate 6:4). Colorless oil, yield 83%. IR (cm^{-1}): ν_{max} 699, 737, 1164, 1366, 1451, 1513, 1667, 1722, 1740, 3330. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.81-0.96 (2H, m, 2 x C<u>H</u>(H)$_{cycl,\ isomer\ 1\ and\ 2}$), 1.38 (6H, d, *J* = 7.1 Hz, 2 x C<u>H$_3$</u>CH$_{isomer\ 1\ and\ 2}$), 1.44 (18H, s, 2 x *t*-Bu$_{isomer\ 1\ and\ 2}$), 1.74-2.07 (4H, m, 2 x CH(<u>H</u>)$_{cycl,\ isomer\ 1\ and\ 2}$ and 2 x CH$_{cycl,\ isomer\ 1\ and\ 2}$), 2.40-2.62 (2H, m, 2 x CHC<u>H</u>(H)N$_{isomer\ 1\ and\ 2}$), 2.70-2.94 (2H, m, 2 x CHCH(<u>H</u>)N$_{isomer\ 1\ and\ 2}$), 3.32-3.58 (4H, m, 4 x NC<u>H</u>(H)Ph$_{isomer\ 1\ and\ 2}$), 3.68 (3H, s, OCH$_{3,\ isomer\ 1}$), 3.74 (3H, s, OCH$_{3,\ isomer\ 2}$), 3.89-4.18 (4H, m, 4 x NCH(<u>H</u>)Ph$_{isomer\ 1\ and\ 2}$), 4.55 (2H, quintet, *J* = 7.1 Hz, 2 x C<u>H</u>CH$_{3,\ isomer\ 1\ and\ 2}$), 6.38 (2H, br s, 2 x NH$_{isomer\ 1\ and\ 2}$), 6.93-7.15 (2H, m, 2 x NH$_{isomer\ 1\ and\ 2}$), 7.20-7.52 (20H, m, 20 x CH$_{arom,\ isomer\ 1\ and\ 2}$). ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.3 and 18.5 (2 x <u>C</u>H$_3$CH$_{isomer\ 1\ and\ 2}$), 23.1 (2 x CH$_{cycl,\ isomer\ 1\ and\ 2}$ and 2 x CH$_{2,\ cycl,\ isomer\ 1\ and\ 2}$), 28.2 (2 x C(<u>C</u>H$_3$)$_{3,\ isomer\ 1\ and\ 2}$), 39.3 (2 x C$_{q,\ cycl,\ isomer\ 1\ and\ 2}$), 48.4 (2 x CH$_3$<u>C</u>H$_{isomer\ 1\ and\ 2}$), 52.2 and 52.3 (2 x OCH$_{3,\ isomer\ 1\ and\ 2}$), 53.0 (2 x CH<u>C</u>H$_2$N$_{isomer\ 1\ and\ 2}$), 57.9 (4 x NCH$_2$Ph$_{isomer\ 1\ and\ 2}$), 80.2 and 80.3 (2 x <u>C</u>(CH$_3$)$_{3,\ isomer\ 1\ and\ 2}$), 127.0, 127.8, 128.2, 128.6, 129.5 (20 x CH$_{arom,\ isomer\ 1\ and\ 2}$), 139.2 (4 x C$_{arom,\ isomer\ 1\ and\ 2}$), 155.9 (2 x NHC=OO$_{isomer\ 1\ and\ 2}$), 171.4 (2 x C=O$_{isomer\ 1\ and\ 2}$), 173.1 and 173.2 (2 x C=O$_{isomer\ 1\ and\ 2}$). MS (ES, pos. mode) *m/z* (%): 496 (M + H$^+$, 100). HRMS (ES) calcd for $C_{28}H_{38}N_3O_5^+$: 496.2806 MH$^+$; found: 496.2808.

(*S*)-methyl 2-{1-(benzyloxycarbonylamino)-2-[(dibenzylamino)methyl]cyclopropanecarboxamido}-propanoate 237.

Spectral data were obtained from a mixture of two diastereomers in a 1:1 ratio.



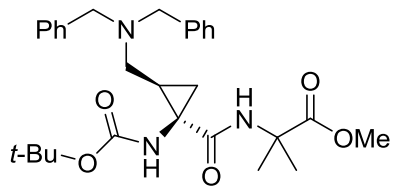
237

R_f = 0.27 (petroleum ether/ethyl acetate 6:4). Colorless oil, yield 83%. IR (cm^{-1}): ν_{max} 697, 737, 1220, 1451, 1495, 1514, 1665, 1736, 3335. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.81-0.95 (2H, m, 2 x C<u>H</u>(H)$_{cycl,\ isomer\ 1\ and\ 2}$), 1.36 (6H, d, *J* = 7.1 Hz, 2 x C<u>H$_3$</u>CH$_{isomer\ 1\ and\ 2}$), 1.83-2.04 (4H, m, 2 x CH(<u>H</u>)$_{cycl,\ isomer\ 1\ and\ 2}$ and 2 x CH$_{cycl,\ isomer\ 1\ and\ 2}$), 2.26-2.44 (2H, m, 2 x CHC<u>H</u>(H)N$_{isomer\ 1\ and\ 2}$), 2.73-2.90 (2H, m, 2 x CHCH(<u>H</u>)N$_{isomer\ 1\ and\ 2}$), 3.10 (4H, d, *J* = 13.1 Hz, 4 x NC<u>H</u>(H)Ph$_{isomer\ 1\ and\ 2}$), 3.65 (3H, s, OCH$_{3,\ isomer\ 1}$), 3.73 (3H, s, OCH$_{3,\ isomer\ 2}$), 3.94 (2H, d, *J* = 13.1 Hz, 2 x NCH(<u>H</u>)Ph$_{isomer\ 1\ and\ 2}$), 3.95 (2H, d, *J* = 13.1 Hz, 2 x NCH(<u>H</u>)Ph$_{isomer\ 1\ and\ 2}$), 4.46-4.63 (2H, m, 2 x C<u>H</u>CH$_{3,\ isomer\ 1\ and\ 2}$), 4.95-5.22 (4H, m, 2 x OCH$_{2,\ isomer\ 1\ and\ 2}$), 6.56 and 6.69 (2 x 1H, 2 x br s, 2 x NH$_{isomer\ 1\ and\ 2}$), 6.92 and 6.96 (2 x 1H, 2 x s, 2 x NH$_{isomer\ 1\ and\ 2}$), 7.20-7.52 (30H, m, 30 x CH$_{arom,\ isomer\ 1\ and\ 2}$). MS (ES, pos. mode) *m/z* (%): 530 (M + H^+, 100). HRMS (ES) calcd for $C_{31}H_{36}N_3O_5^+$: 530.2649 MH^+; found: 530.2648.

Ethyl 2-{1-(*tert*-butoxycarbonylamino)-2-[(dibenzylamino)methyl]cyclopropanecarboxamido}-acetate (±)-243a. R_f = 0.30 (petroleum ether/ethyl acetate 6:4). Colorless oil, yield 85%. IR (cm^{-1}): ν_{max} 698, 743, 1165, 1367, 1521, 1666, 1721, 3339. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.77-0.90 (1H, m, C<u>H</u>(H)$_{cycl}$), 1.25 (3H, t, *J* = 7.1 Hz, OCH$_2$C<u>H$_3$</u>), 1.43 (9H, s, *t*-Bu), 1.76-2.01 (2H, m, CH(<u>H</u>)$_{cycl}$ and CH$_{cycl}$), 2.42 (1H, dxd, *J* = 12.8 Hz, 9.1 Hz, CHC<u>H</u>(H)N), 2.78 (1H, dxd, *J* = 12.8 Hz, 5.3 Hz, CHCH(<u>H</u>)N), 3.33 (2H, d, *J* = 13.4 Hz, 2 x NC<u>H</u>(H)Ph), 3.84 (2H, d, *J* = 13.4 Hz, 2 x NCH(<u>H</u>)Ph), 3.98 (1H, d, *J* = 4.5 Hz, C<u>H</u>(H)CO$_2$Et), 4.01 (1H, d, *J* = 4.5 Hz, CH(<u>H</u>)CO$_2$Et), 4.19 (2H, q, *J* = 7.1 Hz, OC<u>H$_2$</u>CH$_3$), 6.20 and 6.96 (2 x 1H, 2 x br s, 2 x NH), 7.15-7.45 (10H, m, 10 x CH$_{arom}$). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1 (OCH$_2$<u>C</u>H$_3$), 23.9 and 24.3 (CH$_{cycl}$ and CH$_{2,cycl}$), 28.3 (C(<u>C</u>H$_3$)$_3$), 39.1 (C$_{q,\ cycl}$), 41.9 (NHCH$_2$), 54.3 (CH<u>C</u>H$_2$N), 58.4 (2 x NCH$_2$Ph), 61.4 (O<u>C</u>H$_2$CH$_3$), 80.4 (<u>C</u>(CH$_3$)$_3$), 127.2, 128.5, 129.1 (10 x CH$_{arom}$), 138.4 (2 x C$_{arom}$), 156.0 (NHC=OO), 169.8 and 172.2 (2 x C=O). MS (ES, pos. mode) *m/z* (%): 496 (M + H^+, 100). HRMS (ES) calcd for $C_{28}H_{38}N_3O_5^+$: 496.2806 MH^+; found: 496.2808.

(±)-**243a**

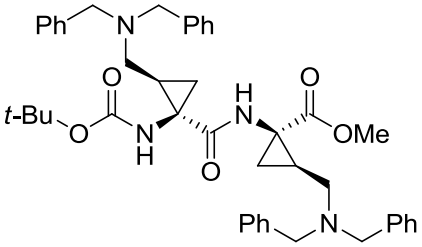
Methyl 2-{1-(*tert*-butoxycarbonylamino)-2-[(dibenzylamino)methyl]cyclopropanecarboxamido}-2-methylpropanoate (±)-243b. R_f = 0.28 (petroleum ether/ethyl acetate 7:3). White amorphous solid, yield 81%. Mp 39 ± 1 °C. IR (cm^{-1}): ν_{max} 698, 738, 1159, 1365, 1453, 1513, 1670, 1724, 3335. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.73-0.83 (1H, m, C<u>H</u>(H)$_{cycl}$), 1.46 (9H, s, *t*-Bu), 1.51 (3H, s, <u>C</u>H$_3$CNH), 1.54 (3H, s, <u>C</u>H$_3$CNH) 1.74-2.03 (2H, m, CH(<u>H</u>)$_{cycl}$ and CH$_{cycl}$), 2.39 (1H, dxd, *J* = 12.1 Hz, 9.1 Hz, CHC<u>H</u>(H)N), 2.77 (1H, dxd, *J* = 12.1 Hz, 4.5 Hz, CHCH(<u>H</u>)N), 3.25 (2H, d, *J* = 13.1 Hz, 2 x NC<u>H</u>(H)Ph), 3.64 (3H, s, OCH$_3$), 3.94 (2H, d, *J* = 13.1 Hz, 2 x NCH(<u>H</u>)Ph), 6.33 and 7.12 (2 x 1H, 2 x br s, 2 x NH), 7.22-7.42 (10H, m, 10 x CH$_{arom}$). ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.2 and 23.5 (CH$_{cycl}$ and CH$_{2,\ cycl}$), 24.5 and 25.1 ((<u>C</u>H$_3$)$_2$C), 28.3 (C(<u>C</u>H$_3$)$_3$), 39.1 (C$_{q,\ cycl}$), 52.3 (OCH$_3$), 53.8 (CH<u>C</u>H$_2$N), 56.4 (CH$_3$)$_2$<u>C</u>), 58.0 (2 x NCH$_2$Ph), 80.2 (<u>C</u>(CH$_3$)$_3$), 127.2, 128.4, 129.1 (10 x CH$_{arom}$), 138.3 (2 x C$_{arom}$), 155.9 (NHC=OO), 171.4 and 174.8 (2 x C=O). MS (ES, pos. mode) *m/z* (%): 510 (M + H$^+$, 100). HRMS (ES) calcd for $C_{29}H_{40}N_3O_5^+$: 510.2962 MH$^+$; found: 510.2971.


(±)-**243b**

Methyl 1-{1-(*tert*-butoxycarbonylamino)-2-[(dibenzylamino)methyl]cyclopropanecarboxamido}-2-[(dibenzylamino)methyl]cyclopropanecarboxylate 254.

Spectral data were obtained from a mixture of two diastereomers in a 1:1 ratio.

R_f = 0.29 (petroleum ether/ethyl acetate 6:4). White amorphous solid, yield 81%. Mp 60 ± 1 °C. IR (cm^{-1}): ν_{max} 697, 744, 1160, 1452, 1492, 1682, 1724, 3387. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.78-0.97 (4H, m, 2 x C<u>H</u>(H)CCO$_2$Me$_{isomer\ 1\ and\ 2}$ and 2 x C<u>H</u>(H)CNHBoc$_{isomer\ 1\ and\ 2}$), 1.35 (9H, s, *t*-Bu$_{isomer\ 1}$), 1.41 (9H, s, *t*-Bu$_{isomer\ 2}$), 1.71-2.09 (8H, m, 2 x CH(<u>H</u>)CCO$_2$Me$_{isomer\ 1\ and\ 2}$, 2 x CH(<u>H</u>)CNHBoc$_{isomer\ 1\ and\ 2}$, 2 x C<u>H</u>CCO$_2$Me$_{isomer\ 1\ and\ 2}$ and 2 x C<u>H</u>CNHBoc$_{isomer\ 1\ and\ 2}$), 2.30-2.92 (8H, m, 4 x CHC<u>H$_2$</u>N$_{isomer\ 1\ and\ 2}$), 3.19-4.12 (16H, m, 8 x NCH$_2$Ph$_{isomer\ 1\ and\ 2}$), 3.68 (6H, s, OCH$_{3,\ isomer\ 1\ and\ 2}$), 6.02 (2H, br s, 2 x NH$_{isomer\ 1\ and\ 2}$), 6.50 (2H, m, 2 x NH$_{isomer\ 1\ and\ 2}$), 7.06-7.49 (40H, m, 40 x CH$_{arom,\ isomer\ 1\ and\ 2}$). MS (ES, pos. mode) *m/z* (%): 717 (M + H$^+$, 100). HRMS (ES) calcd for $C_{44}H_{53}N_4O_5^+$: 717.4010 MH$^+$; found: 717.4044.

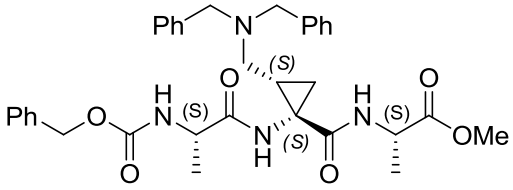

254

5.19 Synthesis of tripeptides 232, (±)-246a and (±)-246b

The synthesis of (*S*)-methyl 2-{(*1S,2S*)-1-[(*S*)-2-(benzyloxycarbonylamino)propanamido]-2-[(dibenzylamino)methyl]cyclopropanecarboxamido}propanoate and (*S*)-methyl 2-{(*1R,2R*)-1-[(*S*)-2-(benzyloxycarbonylamino)propanamido]-2-[(dibenzylamino)methyl]cyclopropanecarboxamido}-propanoate **232a** and **232b** is representative. (*S*)-Methyl 2-{1-(*tert*-butoxycarbonylamino)-2-

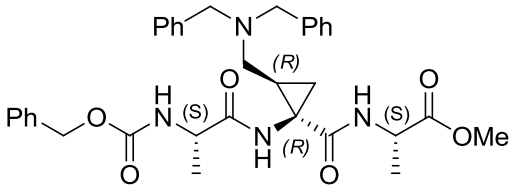
[(dibenzylamino)methyl]cyclopropanecarboxamido}propanoate **238** (100 mg, 0.202 mmol) was dissolved in a 1:1 mixture of TFA/CH_2Cl_2 and the resulting mixture was stirred for one hour at room temperature. The solvent was evaporated in vacuo and the obtained TFA-salt **239** was used without further purification in the next step. To a solution of (*S*)-(benzyloxycarbonyl)alanine **241** (2 equiv, 0.404 mmol, 90 mg) in dry CH_2Cl_2 (5 mL) was added HOAt (2 equiv, 0.404 mmol, 55 mg) and the resulting mixture was allowed to stir for five minutes at room temperature, after which EDC.HCl (2 equiv, 0.404 mmol, 77 mg) was added in one portion. Again the reaction mixture was stirred for five minutes, followed by the addition of TFA-salt **239** (0.202 mmol) and Et_3N until a pH ≈ 8 of the solution was obtained. The reaction mixture was allowed to stir for 16 hours at room temperature and the solvent was evaporated in vacuo. The crude product was purified by column chromatography to yield 32 mg (0.053 mmol) and 26 mg (0.043 mmol) of (*S*)-methyl 2-{(1*S*,2*S*)-1-[(*S*)-2-(benzyloxycarbonylamino)propanamido]-2-[(dibenzylamino)methyl]cyclopropanecarboxamido}-propanoate and (*S*)-methyl 2-{(1*R*,2*R*)-1-[(*S*)-2-(benzyloxycarbonylamino)propanamido]-2-[(dibenzylamino)methyl]cyclopropanecarboxamido}propanoate **232a** and **232b** or vice versa.

(*S*)-methyl 2-{(1*S*,2*S*)-1-[(*S*)-2-(benzyloxycarbonylamino)propanamido]-2-[(dibenzylamino)methyl]-cyclopropanecarboxamido}propanoate or (*S*)-methyl 2-{(1*R*,2*R*)-1-[(*S*)-2-(benzyloxycarbonyl-amino)propanamido]-2-[(dibenzylamino)methyl]cyclopropanecarboxamido}propanoate 232a or 232b. R_f = 0.24 (CH_2Cl_2/MeOH 10:0.2). White amorphous solid, yield 26%. Mp 60 ± 1.0 °C. $[\alpha]_D$ +11.1



232a

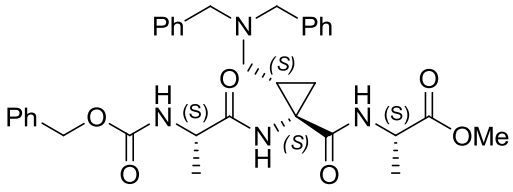
or



232b

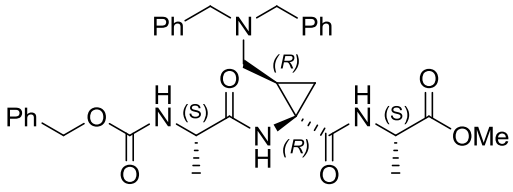
(*c* 0.2, MeOH). IR (cm^{-1}): ν_{max} 698, 737, 1255, 1529, 1668, 1700, 1739, 3344. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.73 (1H, dxd, *J* = 5.6 Hz, 4.5 Hz, C<u>H</u>(H)$_{cycl}$), 0.82 (3H, d, *J* = 6.6 Hz, C<u>H$_3$</u>CH), 1.37 (3H, d, *J* = 7.1 Hz, C<u>H$_3$</u>CH), 1.87-2.10 (2H, m, CH(<u>H</u>)$_{cycl}$ and CH_{cycl}), 2.36 (1H, dxd, *J* = 12.9 Hz, 9.6 Hz, CHC<u>H</u>(H)N), 2.84 (1H, dxd, *J* = 12.9 Hz, 5.1 Hz, CHCH(<u>H</u>)N), 3.18 (2H, d, *J* = 13.1 Hz, 2 x NC<u>H</u>(H)Ph), 3.51 (3H, s, OCH_3), 4.00 (2H, d, *J* = 13.1 Hz, 2 x NCH(<u>H</u>)Ph), 4.52 (1H, quintet, *J* = 7.1 Hz, CH_3C<u>H</u>), 5.05 (1H, d, *J* = 12.4 Hz, OC<u>H</u>(H)Ph), 5.17 (1H, d, *J* = 12.4 Hz, OCH(<u>H</u>)Ph), 5.04-5.18 (1H, m, CH_3C<u>H</u>), 7.23-7.40 (15H, m, 15 x CH_{arom}). ^{13}C NMR (50 MHz, $CDCl_3$): δ 17.0 and 17.4 (2 x CH<u>C</u>H$_3$), 23.0 and 23.2 ($CH_{2,\ cycl}$ and CH_{cycl}), 38.1 ($C_{q,\ cycl}$), 48.6 and 51.1 (2 x <u>C</u>HCH$_3$), 51.9 (OCH_3), 53.5 (CH<u>C</u>H$_2$N), 58.3 (2 x NCH_2Ph), 67.1 (OCH_2Ph), 127.4, 128.0, 128.3, 128.6 and 129.5 (15 x CH_{arom}), 136.0 and 138.7 (3 x C_{arom}), 156.3 (NHC=OO), 170.7, 173.2, 173.9 (3 x C=O). MS (ES, pos. mode) *m/z* (%): 601 (M + H^+, 100). HRMS (ES) calcd for $C_{34}H_{41}N_4O_6^+$: 601.3021 MH^+; found: 601.3049.

(*S*)-methyl 2-{(1*S*,2*S*)-1-[(*S*)-2-(benzyloxycarbonylamino)propanamido]-2-[(dibenzylamino)methyl]-cyclopropanecarboxamido}propanoate or (*S*)-methyl 2-{(1*R*,2*R*)-1-[(*S*)-2-(benzyloxycarbonyl-amino)propanamido]-2-[(dibenzylamino)methyl]cyclopropanecarboxamido}propanoate 232a or



232a

or



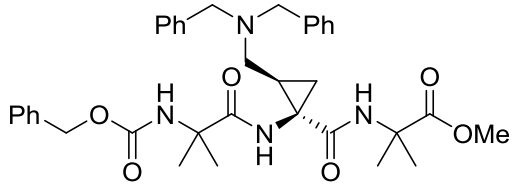
232b

232b. R_f = 0.16 (CH_2Cl_2/MeOH 10:0.2). White amorphous solid, yield 21%. Mp 111 ± 1.0 °C. $[\alpha]_D$ -100.9 (*c* 0.2, MeOH). IR (cm^{-1}): ν_{max} 697, 740, 1203, 1239, 1253, 1530, 1665, 1701, 1733, 3339. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.76-0.90 (1H, m, C<u>H</u>(H)$_{cycl}$), 1.17 (3H, d, *J* = 6.6 Hz, C<u>H$_3$</u>CH), 1.37 (3H, d, *J* = 7.1 Hz, C<u>H$_3$</u>CH), 1.87 (1H, dxd, *J* = 9.1 Hz, 4.5 Hz, CH(<u>H</u>)$_{cycl}$), 1.95-2.14 (1H, m, CH$_{cycl}$), 2.46 (1H, dxd, *J* = 12.9 Hz, 8.3 Hz, CHC<u>H</u>(H)N), 2.73 (1H, dxd, *J* = 12.9 Hz, 5.8 Hz, CHCH(<u>H</u>)N), 3.28 (2H, d, *J* = 13.4 Hz, 2 x NC<u>H</u>(H)Ph), 3.71 (3H, s, OCH_3), 3.87 (2H, d, *J* = 13.4 Hz, 2 x NCH(<u>H</u>)Ph), 4.48 (1H, quintet, *J* = 7.1 Hz, CH_3C<u>H</u>), 5.04 (1H, d, *J* = 12.4 Hz, OC<u>H</u>(H)Ph), 5.18 (1H, d, *J* = 12.4 Hz, OCH(<u>H</u>)Ph), 5.03-5.18 (1H, m, CH_3C<u>H</u>), 7.16-7.39 (15H, m, 15 x CH$_{arom}$). ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.1 and 18.4 (2 x CH<u>C</u>H$_3$), 23.0 and 23.5 (CH$_{2,cycl}$ and CH$_{cycl}$), 38.1 (C$_{q,\ cycl}$), 48.5 and 50.8 (2 x <u>C</u>HCH$_3$), 52.3 (OCH_3), 53.4 (CH<u>C</u>H$_2$N), 58.2 (2 x NCH_2Ph), 67.0 (OCH_2Ph), 127.5, 128.0, 128.3, 128.5 and 129.3 (15 x CH$_{arom}$), 136.1 and 138.6 (3 x C$_{arom}$), 155.9 (NHC=OO), 170.6, 173.2, 173.7 (3 x C=O). MS (ES, pos. mode) *m/z* (%): 601 (M + H^+, 100). HRMS (ES) calcd for $C_{34}H_{41}N_4O_6^+$: 601.3021 MH^+; found: 601.3040.

Ethyl 2-{1-[2-(benzyloxycarbonylamino)acetamido]-2-[(dibenzylamino)methyl]cyclopropane-carboxamido}acetate (±)-246a. R_f = 0.25 (petroleum ether/ethyl acetate 2:8). White amorphous solid, yield 63%. Mp 47 ± 1.0 °C. IR (cm^{-1}): ν_{max} 697, 748, 1193, 1260, 1522, 1668, 1699, 3314. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.81-0.94 (1H, m, C<u>H</u>(H)$_{cycl}$), 1.22 (3H, t, *J* = 7.1 Hz, OCH_2C<u>H$_3$</u>), 1.88 (1H, dxd, *J* = 9.1 Hz, 4.5 Hz, CH(<u>H</u>)$_{cycl}$), 1.99-2.14 (1H, m, CH$_{cycl}$), 2.26-2.50 (1H, m, CHC<u>H</u>(H)N), 2.82 (1H, dxd, *J* = 13.1 Hz, 5.1 Hz, CHCH(<u>H</u>)N), 3.26 (2H, d, *J* = 12.6 Hz, 2 x NC<u>H</u>(H)Ph), 3.95 (2H, d, *J* = 12.6 Hz, 2 x NCH(<u>H</u>)Ph), 3.11-4.08 (4H, m, 2 x NHC<u>H$_2$</u>) 4.14 (2H, q, *J* = 7.6 Hz, $OC\underline{H_2}CH_3$), 5.09 (1H, d, *J* = 12.4 Hz, OC<u>H</u>(H)Ph), 5.16 (1H, d, *J* = 12.4 Hz, OCH(<u>H</u>)Ph), 7.25-7.40 (15H, m, 15 x CH$_{arom}$). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1 ($OCH_2\underline{C}H_3$), 15.2 and 21.3 (CH$_{cycl}$ and CH$_{2,cycl}$), 38.7 (C$_{q,\ cycl}$), 41.8 and 45.1 (2 x $NHCH_2$), 52.8 (CH<u>C</u>H$_2$N), 57.1 (2 x NCH_2Ph), 61.1 (O<u>C</u>H$_2$CH$_3$), 67.0 (OCH_2Ph), 127.9, 128.0, 128.4, 129.1 and 130.6 (15 x CH$_{arom}$), 136.4 (3 x C$_{arom}$), 157.3 (NHC=OO), 169.8

and 170.6 (3 x C=O). MS (ES, pos. mode) *m/z* (%): 587 (M + H^+, 100). HRMS (ES) calcd for $C_{33}H_{39}N_4O_6^+$: 587.2864 MH^+; found: 587.2869.

methyl 2-{1-(2-(benzyloxycarbonylamino)-2-methylpropanamido)-2-[(dibenzylamino)methyl]-cyclopropanecarboxamido}-2-methylpropanoate (±)-246b. R_f = 0.2 (petroleum ether/ethyl acetate 7:3). White amorphous solid, yield 38%. Mp_1 100 ± 1.0 °C and MP_2 134 ± 1.0 °C. IR (cm^{-1}): ν_{max} 698, 737, 1152, 1265, 1530, 1663, 1705, 1738, 3345. ^{1}H NMR (200 MHz, $CDCl_3$): *δ* 0.46 (1H, dxd, *J* = 6.6 Hz, 4.0 Hz, C<u>H</u>(H)$_{cycl}$), 0.73-1.77 (12H, m, 2 x $(CH_3)_2$C<u></u>), 1.80-2.06 (2H, m, CH(<u>H</u>)$_{cycl}$ and CH_{cycl}), 2.40 (1H, dxd, *J* = 13.1 Hz, 9.6 Hz, CHC<u>H</u>(H)N), 2.76 (1H, dxd, *J* = 13.1 Hz, 5.6 Hz, CHCH(<u>H</u>)N), 3.28 (2H, d, *J* = 13.1 Hz, 2 x NC<u>H</u>(H)Ph), 3.61 (3H, s, OCH_3), 3.93 (2H, d, *J* = 13.1 Hz, 2 x NCH(<u>H</u>)Ph), 5.06 (1H, d, *J* = 12.4 Hz, OC<u>H</u>(H)Ph), 5.26 (1H, d, *J* = 12.4 Hz, OCH(<u>H</u>)Ph), 7.19-7.40 (15H, m, 15 x CH_{arom}), 8.35 (1H, br s, NH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.5 and 22.8 (CH_{cycl} and $CH_{2,\ cycl}$), 25.0, 25.4, 26.8 and 27.5 (2 x (<u>C</u>$H_3)_2$C), 40.5 ($C_{q,\ cycl}$), 51.2 (OCH_3), 52.2 (CH<u>C</u>H_2N), 56.3 and 57.8 (2 x $(CH_3)_2$<u>C</u>), 58.1 (2 x NCH_2Ph), 66.9 (OCH_2Ph), 127.4, 127.7, 128.5, 128.9, 129.4, 129.5, 129.8 and 130.5 (15 x CH_{arom}), 137.8 (3 x C_{arom}), 155.9 (NHC=OO), 169.4 and 172.6 (3 x C=O). MS (ES, pos. mode) *m/z* (%): 629 (M + H^+, 100). HRMS (ES) calcd for $C_{36}H_{45}N_4O_6^+$: 629.3334 MH^+; found: 629.3341.



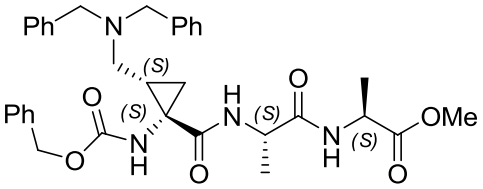
(±)-**246b**

5.20 Synthesis of tripeptides 231, (±)-250 and (±)-253

The synthesis of (*S*)-methyl 2-{(*S*)-2-[(*1S,2S*)-1-(benzyloxycarbonylamino)-2-[(dibenzylamino)methyl]-cyclopropanecarboxamido]propanamido}propanoate and (*S*)-methyl 2-{(*S*)-2-[(*1R,2R*)-1-(benzyloxy-carbonylamino)-2-[(dibenzylamino)methyl]cyclopropanecarboxamido]propanamido}propanoate **231a** and **231b** is representative. To a solution of *cis*-1-(benzyloxycarbonylamino)-2-[(dibenzylamino)methyl]cyclopropane-1-carboxylic acid (±)-**223** (100 mg, 0.225 mmol) in dry CH_2Cl_2 (5 mL) was added HOAt (1 equiv, 0.225 mmol, 30 mg) and the resulting mixture was allowed to stir for five minutes at room temperature, after which EDC.HCl (1 equiv, 0.225 mmol, 43 mg) was added in one portion. Again the reaction mixture was stirred for five minutes, followed by the addition of H-$(Ala)_2$-OMe.TFA **236** (2 equiv, 0.45 mmol) and Et_3N until a pH ≈ 8 of the solution was obtained. The reaction mixture was allowed to stir for 16 hours at room temperature and the solvent was evaporated in vacuo. The crude product was purified by column chromatography to yield 24 mg (0.040 mmol) and 35 mg (0.058 mmol) of (*S*)-methyl 2-{(*S*)-2-[(*1S,2S*)-1-(benzyloxycarbonylamino)-2-[(dibenzylamino)methyl]cyclopropanecarboxamido]propanamido}propanoate and (*S*)-methyl 2-{(*S*)-

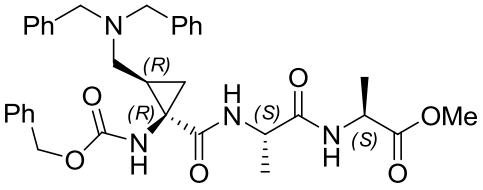
2-[(*1R,2R*)-1-(benzyloxycarbonyl-amino)-2-[(dibenzylamino)methyl]cyclopropanecarboxamido]-propanamido}propanoate **231a** and **231b** or vice versa.

(*S*)-Methyl 2-{(*S*)-2-[(*1S,2S*)-1-(benzyloxycarbonylamino)-2-[(dibenzylamino)methyl]cyclopropane-carboxamido]propanamido}propanoate or (*S*)-methyl 2-{(*S*)-2-[(*1R,2R*)-1-(benzyloxycarbonyl-amino)-2-[(dibenzylamino)methyl]cyclopropanecarboxamido]propanamido}propanoate 231a or



231a

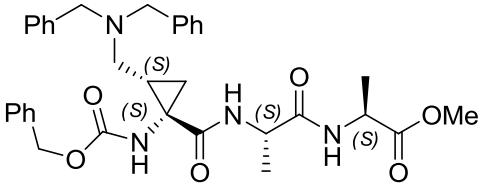
or



231b

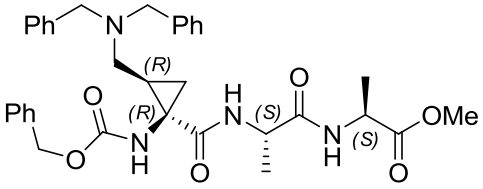
231b. R_f = 0.22 (CH_2Cl_2/MeOH 10:0.2). White amorphous solid, yield 18%. Mp 54 ± 1.0 °C. $[\alpha]_D$ -39.4 (*c* 0.5, MeOH). IR (cm^{-1}): ν_{max} 697, 737, 1227, 1452, 1515, 1644, 1714, 1737, 3312. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.82 (1H, dxd, *J* = 6.1 Hz, 4.0 Hz, C<u>H</u>(H)$_{cycl}$), 1.30-1.43 (6H, m, 2 x C<u>H$_3$</u>CH), 1.87-2.10 (2H, m, CH(<u>H</u>)$_{cycl}$ and CH_{cycl}), 2.36 (1H, dxd, *J* = 12.9 Hz, 9.3 Hz, CHC<u>H</u>(H)N), 2.85 (1H, dxd, *J* = 12.9 Hz, 5.3 Hz, CHCH(<u>H</u>)N), 3.21 (2H, d, *J* = 13.1 Hz, 2 x NC<u>H</u>(H)Ph), 3.73 (3H, s, OCH_3), 3.94 (2H, d, *J* = 13.1 Hz, 2 x NCH(<u>H</u>)Ph), 4.42-4.60 (2H, m, 2 x CH_3C<u>H</u>), 5.00 (1H, d, *J* = 12.6 Hz, OC<u>H</u>(H)Ph), 5.14 (1H, d, *J* = 12.6 Hz, OCH(<u>H</u>)Ph), 6.70 (1H, br s, NH), 6.76-6.95 (2H, m, 2 x NH), 7.12-7.47 (15H, m, 15 x CH_{arom}). ^{13}C NMR (50 MHz, $CDCl_3$): δ 17.8 (2 x CH<u>C</u>H$_3$), 24.2 ($CH_{2,\ cycl}$ and CH_{cycl}), 39.2 ($C_{q,\ cycl}$), 48.1 and 49.0 (2 x <u>C</u>HCH$_3$), 52.3 (OCH_3), 53.9 (CH<u>C</u>H$_2$N), 58.4 (2 x NCH_2Ph), 67.2 (OCH_2Ph), 127.3, 128.1, 128.3, 128.5 and 129.0 (15 x CH_{arom}), 136.1 and 138.1 (3 x C_{arom}), 157.0 (NHC=OO), 171.5, 171.6, 172.9 (3 x C=O). MS (ES, pos. mode) *m/z* (%): 601 (M + H^+, 100). HRMS (ES) calcd for $C_{34}H_{41}N_4O_6^+$: 601.3021 MH^+; found: 601.3045.

(*S*)-Methyl 2-{(*S*)-2-[(*1S,2S*)-1-(benzyloxycarbonylamino)-2-[(dibenzylamino)methyl]cyclopropanecarboxamido]propanamido}propanoate or (*S*)-methyl 2-{(*S*)-2-[(*1R,2R*)-1-(benzyloxycarbonylamino)-2-[(dibenzylamino)methyl]cyclopropanecarboxamido]propanamido}propanoate 231a or



231a

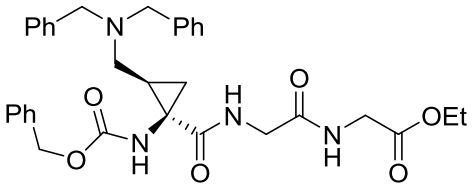
or



231b

231b. R_f = 0.16 (CH_2Cl_2/MeOH 10:0.2). White amorphous solid, yield 26%. Mp 51 ± 1.0 °C. $[\alpha]_D$ +19.4 (*c* 0.2, MeOH). IR (cm^{-1}): ν_{max} 697, 737, 1227, 1451, 1514, 1647, 1737, 3312. ^{1}H NMR (200 MHz, $CDCl_3$): *δ* 0.86 (1H, dxd, *J* = 6.6 Hz, 4.5 Hz, C<u>H</u>(H)$_{cycl}$), 1.19 (3H, d, *J* = 7.1 Hz, C<u>H$_3$</u>CH), 1.33 (3H, d, *J* = 7.1 Hz, C<u>H$_3$</u>CH), 1.84-2.10 (2H, m, CH(<u>H</u>)$_{cycl}$ and CH$_{cycl}$), 2.34 (1H, dxd, *J* = 13.2 Hz, 9.9 Hz, CHC<u>H</u>(H)N), 2.80 (1H, dxd, *J* = 13.2 Hz, 5.3 Hz, CHCH(<u>H</u>)N), 3.20 (2H, d, *J* = 13.1 Hz, 2 x NC<u>H</u>(H)Ph), 3.72 (3H, s, OCH_3), 3.91 (2H, d, *J* = 13.1 Hz, 2 x NCH(<u>H</u>)Ph), 4.45 (2H, quintet, *J* = 7.1 Hz, 2 x CH_3C<u>H</u>), 5.01 (1H, d, *J* = 12.4 Hz, OC<u>H</u>(H)Ph), 5.11 (1H, d, *J* = 12.4 Hz, OCH(<u>H</u>)Ph), 6.52 (1H, br s, NH), 6.67 (1H, d, *J* = 6.6 Hz, NH), 6.95 (1H, d, *J* = 7.6 Hz, NH), 7.15-7.41 (15H, m, 15 x CH$_{arom}$). ^{13}C NMR (50 MHz, $CDCl_3$): *δ* 17.8 and 17.9 (2 x CH<u>C</u>H$_3$), 23.8 and 24.5 (CH$_{2,\ cycl}$ and CH$_{cycl}$), 39.2 (C$_{q,\ cycl}$), 48.0 and 49.1 (2 x <u>C</u>HCH$_3$), 52.3 (OCH_3), 53.7 (CH<u>C</u>H$_2$N), 58.4 (2 x NCH_2Ph), 67.1 (OCH_2Ph), 127.3, 128.2, 128.5 and 129.0 (15 x CH$_{arom}$), 136.2 and 138.0 (3 x C$_{arom}$), 156.7 (NHC=OO), 171.5, 171.8, 170.0 (3 x C=O). MS (ES, pos. mode) *m/z* (%): 601 (M + H^+, 100). HRMS (ES) calcd for $C_{34}H_{41}N_4O_6^+$: 601.3021 MH^+; found: 601.3017.

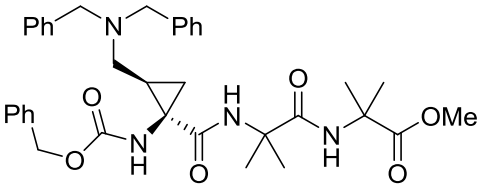
Ethyl 2-{2-[1-(benzyloxycarbonylamino)-2-[(dibenzylamino)methyl]cyclopropanecarboxamido]-acetamido}acetate (±)-250. R_f = 0.45 (petroleum ether/ethyl acetate 2:8). White amorphous solid, yield 78%. Mp 42 ± 1.0 °C. IR (cm^{-1}): ν_{max} 697, 737, 1201, 1236, 1523, 1661, 1708, 1736, 3329. ^{1}H NMR (200 MHz, $CDCl_3$): *δ* 0.81-0.93 (1H, m, C<u>H</u>(H)$_{cycl}$), 1.24 (3H, t, *J* = 7.1 Hz, OCH_2C<u>H$_3$</u>), 1.87-2.03 (2H, m, CH(<u>H</u>)$_{cycl}$ and CH$_{cycl}$), 2.36 (1H, dxd, *J* = 12.6 Hz, 8.6 Hz, CHC<u>H</u>(H)N), 2.84 (1H, dxd, *J* = 12.6 Hz, 5.1 Hz, CHCH(<u>H</u>)N), 3.23 (2H, d, *J* = 13.4 Hz, 2 x NC<u>H</u>(H)Ph), 3.88 (2H, d, *J* = 13.4 Hz, 2 x NCH(<u>H</u>)Ph), 3.71-3.93 (2H, m, NHC<u>H$_2$</u>) 4.14 (2H, q, *J* = 7.1 Hz, OC<u>H$_2$</u>CH$_3$), 4.00-4.23 (2H, m, NHC<u>H$_2$</u>), 5.00 (1H, d, *J* = 12.4 Hz, OC<u>H</u>(H)Ph), 5.08 (1H, d, *J* = 12.4 Hz, OCH(<u>H</u>)Ph), 6.81 (1H, br s, NH), 7.09-7.42 (15H, m, 15 x CH$_{arom}$). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1 (OCH_2C<u>H$_3$</u>), 24.3 (CH$_{cycl}$ and CH$_{2,cycl}$), 39.3 (C$_{q,\ cycl}$), 41.0 and 43.3 (2 x $NHCH_2$), 54.3 (CH<u>C</u>H$_2$N), 58.7 (2 x NCH_2Ph), 61.4 (O<u>C</u>H$_2$CH$_3$), 67.4 (OCH_2Ph), 127.3, 128.4, 128.6 and 128.9 (15 x CH$_{arom}$), 135.9 and 138.2 (3 x C$_{arom}$), 157.4 (NHC=OO), 169.5,



(±)-**250**

169.7, 172.1 (3 x C=O). MS (ES, pos. mode) *m/z* (%): 587 (M + H^+, 100). HRMS (ES) calcd for $C_{33}H_{39}N_4O_6^+$: 587.2864 MH^+; found: 587.2873.

Methyl 2-{2-[1-(benzyloxycarbonylamino)-2-[(dibenzylamino)methyl]cyclopropanecarboxamido]-2-methylpropanamido}-2-methylpropanoate (±)-253. R_f = 0.38 (petroleum ether/ethyl acetate 4:6). White amorphous solid, yield 50%. Mp 125 ± 1.0 °C. IR (cm^{-1}): ν_{max} 697, 737, 1151, 1245, 1519, 1669, 1707, 1738, 3345. ^{1}H NMR (200 MHz, $CDCl_3$): *δ* 0.71-0.79 (1H, m, C<u>H</u>(H)$_{cycl}$), 1.36 (3H, s, <u>C</u>H_3CNH), 1.45 (9H, s, 3 x <u>C</u>H_3CNH), 1.84-2.04 (2H, m, CH(<u>H</u>)$_{cycl}$ and CH_{cycl}), 2.34 (1H, dxd, *J* = 12.9 Hz, 9.1 Hz, CHC<u>H</u>(H)N), 2.83 (1H, dxd, *J* = 12.9 Hz, 5.6 Hz, CHCH(<u>H</u>)N), 3.20 (2H, d, *J* = 13.1 Hz, 2 x NC<u>H</u>(H)Ph), 3.67 (3H, s, OCH_3), 3.95 (2H, d, *J* = 13.1 Hz, 2 x NCH(<u>H</u>)Ph), 4.98 (1H, d, *J* = 12.4 Hz, OC<u>H</u>(H)Ph), 5.17 (1H, d, *J* = 12.4 Hz, OCH(<u>H</u>)Ph), 6.71, 6.83 and 7.12 (3 x 1H, 3 x br s, 3 x NH), 7.20-7.42 (15H, m, 15 x CH_{arom}). ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.6 (CH_{cycl} and $CH_{2,\ cycl}$), 24.3, 25.1 and 26.3 (2 x (<u>C</u>H_3)$_2$C), 39.6 ($C_{q,\ cycl}$), 52.3 (OCH_3), 53.5 (CH<u>C</u>H_2N), 56.0 and 57.2 (2 x (CH_3)$_2$<u>C</u>), 58.2 (2 x NCH_2Ph), 67.1 (OCH_2Ph), 127.4, 128.3, 128.4, 128.6 and 129.0 (15 x CH_{arom}), 136.2 and 138.0 (3 x C_{arom}), 157.1 (NHC=OO), 171.0, 173.4, 175.0 (3 x C=O). MS (ES, pos. mode) *m/z* (%): 629 (M + H^+, 100). HRMS (ES) calcd for $C_{36}H_{45}N_4O_6^+$: 629.3334 MH^+; found: 629.3332.

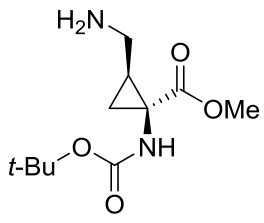


(±)-**253**

5.21 Synthesis of methyl 2-(aminomethyl)-1-(*tert*-butoxycarbonylamino)-cyclopropanecarboxylate (±)-261

To a solution of *cis*-methyl 1-*tert*-butoxycarbonylamino-2-[(dibenzylamino)methyl]cyclopropane-1-carboxylate (±)-**222** (230 mg, 0.54 mmol) in MeOH was added Pd/C (20% mass fraction, 46 mg) and NH_4HCO_2 (5 equiv, 2.71 mmol, 171 mg). The reaction mixture was stirred for 30 minutes at reflux and subsequently filtered through a syringe filter. The organic phase was evaporated in vacuo to yield 127 mg (0.52 mmol) of methyl 2-(aminomethyl)-1-(*tert*-butoxycarbonylamino)cyclopropane-carboxylate (±)-**261**.

Methyl 2-(aminomethyl)-1-(*tert*-butoxycarbonylamino)cyclopropanecarboxylate (±)-261. White amorphous solid, yield 96%. Mp 126 ± 1 °C. IR (cm^{-1}): ν_{max} 728, 1161, 1691, 1718, 3225. ^{1}H NMR (400 MHz, CD_3OD): δ 1.03 (1H, dxd, *J* = 7.2 Hz, 5.6 Hz, C<u>H</u>(H)$_{cycl}$), 1.38 (9H, s, *t*-Bu), 1.53 (1H, dxd, *J* = 9.8 Hz, 5.6 Hz, CH(<u>H</u>)$_{cycl}$), 2.00-2.11 (1H, m, CH_{cycl}), 2.74 (1H, dxd, *J* = 13.4 Hz, 9.4 Hz, C<u>H</u>(H)NH_2), 3.12 (1H, dxd, *J* = 13.4 Hz, 5.2 Hz, CH(<u>H</u>)NH_2), 3.61 (3H, s, OCH_3). ^{13}C NMR (100 MHz, CD_3OD): δ 19.2 ($CH_{2,\ cycl}$), 24.5 (CH_{cycl}), 27.3 (C(<u>C</u>H_3)$_3$), 37.9 ($C_{q,\ cycl}$), 38.7 (CH_2NH_2),



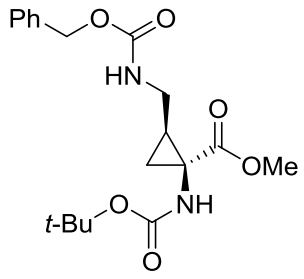
(±)-**261**

51.9 (OCH_3), 80.5 ($\underline{C}(CH_3)_3$), 159.0 (NHC=O), 172.2 (C=O). MS (ES, pos. mode) *m/z* (%): 245 ($M + H^+$, 100). HRMS (ES) calcd for $C_{11}H_{21}N_2O_4^+$: 245.1496 MH^+; found: 245.1495.

5.22 Synthesis of methyl 2-[(benzyloxycarbonylamino)methyl]-1-(*tert*-butoxycarbonylamino)cyclopropanecarboxylate (±)-263

Methyl 2-(aminomethyl)-1-(*tert*-butoxycarbonylamino)cyclopropanecarboxylate (±)-**261** (130 mg, 0.53 mmol) was dissolved in a 1:1 mixture of an aqueous saturated $NaHCO_3$ solution and Et_2O. The solution was cooled to 0 °C and benzyl chloroformate (1.1 equiv, 0.59 mmol, 0.08 mL) was added dropwise. The reaction mixture was allowed to stir for 15 minutes at 0 °C. The aqueous phase was extracted with Et_2O and the combined organic phases were dried ($MgSO_4$), filtered, and evaporated in vacuo. The crude product was purified by column chromatography to yield 114 mg (0.30 mmol) of methyl 2-[(benzyloxycarbonylamino)methyl]-1-(*tert*-butoxycarbonylamino)cyclopropanecarboxylate (±)-**263**.

Methyl 2-[(benzyloxycarbonylamino)methyl]-1-(*tert*-butoxycarbonylamino)cyclopropanecarboxylate (±)-263. R_f = 0.25 (petroleum ether/ethyl acetate 7:3). White amorphous solid, yield 57%. Mp 128 ± 0.5 °C. IR (cm^{-1}): ν_{max} 1158, 1249, 1281, 1508, 1684, 1728, 3338. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (1H, dxd, *J* = 7.2 Hz, 5.4 Hz, $C\underline{H}(H)_{cycl}$), 1.45 (9H, s, *t*-Bu), 1.59 (1H, dxd, *J* = 9.6 Hz, 5.4 Hz, $CH(\underline{H})_{cycl}$), 1.92-2.02 (1H, m, CH_{cycl}), 2.69-2.83 (1H, m, $C\underline{H}(H)NH$), 3.67 (3H, s, OCH_3), 3.72-3.83 (1H, m, $CH(\underline{H})NH$), 5.09 (1H, d, *J* = 12.8 Hz, $OC\underline{H}(H)Ph$), 5.12 (1H, d, *J* = 12.8 Hz, $OCH(\underline{H})Ph$), 5.81 and 5.94 (2 x 1H, 2 x s, 2 x NH), 7.26-7.36 (5H, m, 5 x CH_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.1 ($CH_{2,cycl}$), 28.2 ($C(\underline{C}H_3)_3$), 28.6 (CH_{cycl}), 38.2 ($C_{q,\ cycl}$), 39.9 (CH_2NH), 52.5 (OCH_3), 66.6 (OCH_2Ph), 80.4 ($\underline{C}(CH_3)_3$), 128.0 and 128.4 (5 x CH_{arom}), 136.7 (C_{arom}), 156.7 and 157.2 (2 x NHC=O), 172.9 (C=O). MS (ES, pos. mode) *m/z* (%): 279 ($M + H^+$ - CO_2 - isobutene, 100).



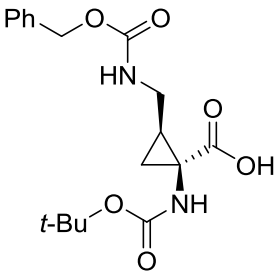
(±)-**263**

5.23 Synthesis of 2-[(benzyloxycarbonylamino)methyl]-1-(*tert*-butoxycarbonylamino)cyclopropanecarboxylic acid (±)-264

Methyl 2-[(benzyloxycarbonylamino)methyl]-1-(*tert*-butoxycarbonylamino)cyclopropanecarboxylate (±)-**263** (84 mg, 0.22 mmol) was treated with 2M aq. NaOH (5 equiv, 0.56 mL) in a 1:3 mixture of 2M NaOH/MeOH. The reaction mixture was stirred for 1 hour at reflux, after which MeOH was evaporated in vacuo. The aqueous phase was brought to pH = 4 with 2M aq. HCl and extracted with EtOAc (3 x 10 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated in vacuo. Precipitation in diethyl ether afforded 75 mg (0.21 mmol) of 2-

[(benzyloxycarbonylamino)methyl]-1-(*tert*-butoxycarbonylamino)cyclopropanecarboxylic acid (±)-**264**.

2-[(Benzyloxycarbonylamino)methyl]-1-(*tert*-butoxycarbonylamino)cyclopropanecarboxylic acid (±)-264. White amorphous solid, yield 94%. Mp 82 ± 0.5 °C. IR (cm^{-1}): ν_{max} 1159, 1248, 1518, 1692, 3329. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86-0.94 (1H, m, C<u>H</u>(H)$_{cycl}$), 1.43 (9H, s, *t*-Bu), 1.59-1.68 (1H, m, CH(<u>H</u>)$_{cycl}$), 1.94-2.08 (1H, m, CH_{cycl}), 2.68-2.92 (1H, m, C<u>H</u>(H)NH), 3.61-3.80 (1H, m, CH(<u>H</u>)NH), 5.09 (2H, s, OCH_2Ph), 5.87 and 5.91 (2 x 1H, 2 x s, 2 x NH), 7.25-7.36 (5H, m, 5 x CH_{arom}), 9.87 (1H, s, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.7 ($CH_{2,\ cycl}$), 28.2 (C(<u>C</u>H_3)$_3$), 29.2 (CH_{cycl}), 37.9 ($C_{q,\ cycl}$), 39.9 (CH_2NH), 66.7 (OCH_2Ph), 80.6 (<u>C</u>(CH_3)$_3$), 127.0, 127.6, 128.0, 128.4 and 128.5 (5 x CH_{arom}), 136.6 (C_{arom}), 156.8 and 157.3 (2 x NHC=O), 177.9 (C=O). MS (ES, pos. mode) *m/z* (%): 265 ($M + H^+ - CO_2$ - isobutene, 100).

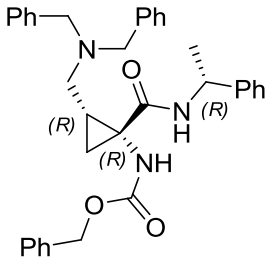


(±)-**264**

5.24 Synthesis of benzyl 2-[(dibenzylamino)methyl]-1-[(*R*)-1-phenylethylcarbamoyl]cyclopropylcarbamate 267

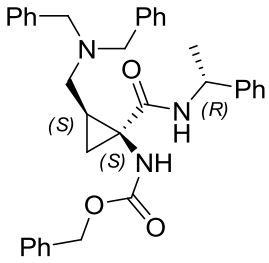
A flame-dried round-bottomed flask was charged with *cis*-1-(benzyloxycarbonylamino)-2-[(dibenzylamino)methyl]cyclopropane-1-carboxylic acid (±)-**223** (532 mg, 1.20 mmol) in anhydrous THF (10 mL) under a nitrogen atmosphere. To the solution was added HOAt (1.01 equiv, 1.21 mmol, 165 mg) and EDC.HCl (1.01 equiv, 1.21 mmol, 232 mg) and the solution was stirred for 5 minutes at room temperature, after which (*R*)-(+)-α-methylbenzylamine (2 equiv, 2.40 mmol, 291 mg) and Et_3N (to pH 8) were added. The reaction mixture was stirred for 16 h, the solvent was evaporated, and the crude product was purified by column chromatography to give benzyl 2-[(dibenzylamino)methyl]-1-[(*R*)-1-phenylethylcarbamoyl]cyclopropylcarbamate **267** as a 1:1 mixture of diastereomers in 69% yield (456 mg, 0.83 mmol). Separation of both diastereomers *via* preparative TLC afforded 145 mg (0.26 mmol) benzyl (*1R,2R*)-2-[(dibenzylamino)methyl]-1-[(*R*)-1-phenylethylcarbamoyl]-cyclopropylcarbamate and 151 mg (0.28 mmol) benzyl (*1S,2S*)-2-[(dibenzylamino)methyl]-1-[(*R*)-1-phenylethylcarbamoyl]-cyclopropylcarbamate **267a** and **267b** or vice versa.

Benzyl (*1R,2R*)-2-[(dibenzylamino)methyl]-1-((*R*)-1-phenylethylcarbamoyl)cyclopropylcarbamate or benzyl (*1S,2S*)-2-[(dibenzylamino)methyl]-1-[(*R*)-1-phenylethylcarbamoyl]cyclopropylcarbamate 267a or 267b. R_f = 0.30 (petroleum ether/ethyl acetate 7:3). Colorless oil, yield 22%. $[\alpha]_D$ +25.7 (*c* 0.52, MeOH). IR (cm^{-1}): ν_{max} 696, 736, 1227, 1494, 1656, 1720, 3329. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.81 (1H, dxd, *J* = 6.8 Hz, 4.5 Hz, C<u>H</u>(H)$_{cycl}$), 1.40 (3H, d, *J* = 6.9 Hz, CH_3), 1.87 (1H, dxd, *J* = 8.6 Hz, 4.5 Hz, CH(<u>H</u>)$_{cycl}$), 1.96-2.06 (1H, m, CH_{cycl}), 2.33 (1H, dxd, *J* = 12.9 Hz, 9.5 Hz, CHC<u>H</u>(H)N), 2.81 (1H, dxd, *J* = 12.9 Hz, 5.3 Hz, CHCH(<u>H</u>)N), 3.17 (2H, d, *J* = 13.1 Hz, NC<u>H</u>(H)Ph), 3.96 (2H, d, *J* = 13.1 Hz, NCH(<u>H</u>)Ph), 4.91 (1H, d, *J* = 12.3 Hz, OC<u>H</u>(H)Ph), 5.00-5.09 (1H, m, C<u>H</u>CH_3), 5.13 (1H, d, *J* = 12.3 Hz, OCH(<u>H</u>)Ph), 6.67-6.78 (2H, m, 2 x NH), 7.17-7.37 (20H, m, 20 x CH_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.1 (CH_3), 23.8 ($CH_{2,\ cycl}$ and CH_{cycl}), 39.2 ($C_{q,\ cycl}$), 48.8 (<u>C</u>HCH_3), 53.9 (CH<u>C</u>H_2N), 58.2 (2 x N<u>C</u>H_2Ph), 67.0 (O<u>C</u>H_2Ph), 125.8, 127.0, 127.3, 128.52, 128.55 and 129.1 (20 x CH_{arom}), 138.1 and 143.4 (4 x C_{arom}), 156.8 (NHC=O), 170.9 (C=O). MS (ES, pos. mode) *m/z* (%): 548 (M + H^+, 100). HRMS (ES) calcd for $C_{35}H_{38}N_3O_3^+$: 548.2908 MH^+; found: 548.2900.



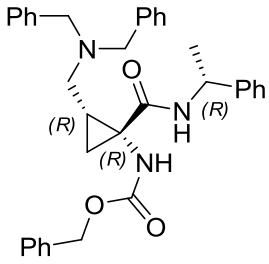
267a

or



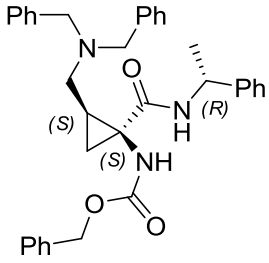
267b

Benzyl (*1R,2R*)-2-[(dibenzylamino)methyl]-1-((*R*)-1-phenylethylcarbamoyl)cyclopropylcarbamate or benzyl (*1S,2S*)-2-[(dibenzylamino)methyl]-1-[(*R*)-1-phenylethylcarbamoyl]cyclopropylcarbamate 267a or 267b. R_f = 0.19 (petroleum ether/ethyl acetate 7:3). White amorphous solid, yield 23%. Mp 141 ± 0.5 °C. $[\alpha]_D$ -36.7 (*c* 0.51, MeOH). IR (cm^{-1}): ν_{max} 694, 747, 1230, 1504, 1525, 1650, 1735, 3244. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.78-0.83 (1H, m, C<u>H</u>(H)$_{cycl}$), 1.32-1.45 (3H, m, CH_3), 1.86-2.03 (2H, m, CH(<u>H</u>)$_{cycl}$ and CH_{cycl}), 2.31 (1H, dxd, *J* = 13.0 Hz, 10.3 Hz, CHC<u>H</u>(H)N), 2.77 (1H, dxd, *J* = 13.0 Hz, 4.8 Hz, CHCH(<u>H</u>)N), 3.07 (2H, d, *J* = 13.1 Hz, NC<u>H</u>(H)Ph), 3.92 (2H, d, *J* = 13.1 Hz, NCH(<u>H</u>)Ph), 4.84-5.27 (3H, m, OC<u>H</u>$_2$Ph and C<u>H</u>CH_3), 6.68 (1H, br d, *J* = 7.6 Hz, NH), 6.75 (1H, br s, NH), 7.08-7.40 (20H, m, 20 x CH_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8 (CH_3), 23.9 ($CH_{2,\ cycl}$ and CH_{cycl}), 39.3 ($C_{q,\ cycl}$), 49.1 (<u>C</u>HCH_3), 54.1 (CH<u>C</u>H_2N), 58.3 (2 x N<u>C</u>H_2Ph), 67.0 (O<u>C</u>H_2Ph), 125.9, 127.1, 127.3, 128.58, 128.60 and 129.0 (20 x CH_{arom}), 136.4, 138.1 and 143.3 (4 x C_{arom}), 156.9 (NHC=O), 170.9 (C=O). MS (ES, pos. mode) *m/z* (%): 548 (M + H^+, 100). HRMS (ES) calcd for $C_{35}H_{38}N_3O_3^+$: 548.2908 MH^+; found: 548.2909.



267a

or

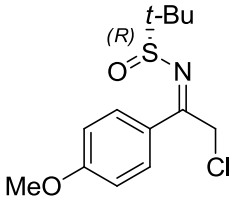


267b

5.25 Synthesis of α-halo-*N*-(*tert*-butanesulfinyl)imines (R_S)-282e and (S_S)-268c

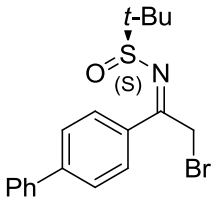
As a representative example, the synthesis of (R_S)-*N*-[2-chloro-1-(4-methoxyphenyl)ethylidene]-*tert*-butanesulfinamide (R_S)-**282e** is described. In a flame-dried flask was made a solution of 2-chloro-4'-methoxyacetophenone (1.00 g, 5.42 mmol) and $Ti(OEt)_4$ (2 equiv, 10.8 mmol, 2.47 g) in dry tetrahydrofuran (30 mL). (R_S)-*tert*-Butanesulfinamide (1 equiv, 5.42 mmol, 0.65 g) was added and the reaction mixture was allowed to stir for 72 hours at reflux. After cooling, brine was added, the resulting mixture was filtered over Celite® and the solids were washed with EtOAc (2 x 10 mL). The solution was extracted with EtOAc (3 x 25 mL), and the combined organic layers were dried ($MgSO_4$), filtered and concentrated. The crude compound was purified by column chromatography to yield 1.33 g (4.62 mmol) (R_S)-*N*-[2-chloro-1-(4-methoxyphenyl)ethylidene]-*tert*-butanesulfinamide (R_S)-**282e** as a yellow liquid.

(R_S)-*N*-[2-Chloro-1-(4-methoxyphenyl)ethylidene]-*tert*-butanesulfinamide (R_S)-282e. R_f = 0.22 (petroleum ether/ethyl acetate 3:1). yellow oil, yield 85%. $[\alpha]_D$ -51.5 (*c* 0.94, CH_2Cl_2). IR (cm^{-1}): ν_{max} 1071, 1255, 1361, 1586, 2960. ^1H NMR (300 MHz, $CDCl_3$): δ 1.35 (9H, s, *t*-Bu), 3.87 (3H, s, OMe), 4.97 (1H, d, *J* = 11.3 Hz, C<u>H</u>(H)Cl), 5.14 (1H, d, *J* = 11.3 Hz, CH(<u>H</u>)Cl), 6.95 and 7.87 (2 x 2H, 2 x d, 2 x *J* = 8.8 Hz, 4 x CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.1 (C(<u>C</u>H_3)$_3$), 35.4 (CH_2Cl), 55.5 (OMe), 59.3 (<u>C</u>$(CH_3)_3$), 114.0 (2 x CH_{arom}), 128.5 (C_{arom}), 129.6 (2 x CH_{arom}), 162.7 (C_{arom}), 168.8 (C=N). MS (ES, pos. mode) *m/z* (%): 288/290 ($M + H^+$, 100).



(R_S)-**282e**

(S_S)-*N*-{1-([1,1'-biphenyl]-4-yl)-2-bromoethylidene}-*tert*-butanesulfinamide (S_S)-268c. R_f = 0.26 (petroleum ether/ethyl acetate 4:1). Brown amorphous solid, yield 39%. Mp 98 ± 0.5 °C. $[\alpha]_D$ -35.4 (*c* 0.54, $CHCl_3$). IR (cm^{-1}): ν_{max} 698, 1065, 1286, 1361, 1552, 1576. ^1H NMR (300 MHz, $CDCl_3$): δ 1.39 (9H, s, *t*-Bu), 4.89 (1H, d, *J* = 9.9 Hz, C<u>H</u>(H)Br), 5.14 (1H, d, *J* = 9.9 Hz, CH(<u>H</u>)Br), 7.36-7.51 (3H, m, 3 x CH_{arom}), 7.63, 7.68 and 7.96 (3 x 2H, 3 x d, 3 x *J* = 7.7 Hz, 6 x CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.5 (CH_2Br), 23.3 (C(<u>C</u>H_3)$_3$), 59.7 (<u>C</u>$(CH_3)_3$), 127.2, 127.4, 127.9, 128.2 and 129.0 (9 x CH_{arom}), 134.8, 139.8 and 144.7 (3 x C_{arom}), 169.1 (C=N). MS (ES, pos. mode) *m/z* (%): 378/380 ($M + H^+$, 100). HRMS (ES) calcd for $C_{18}H_{21}{}^{79}BrNOS^+$: 378.0522 MH^+; found: 378.0517.



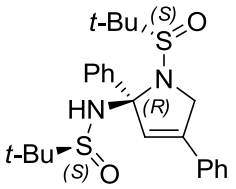
(S_S)-**268c**

5.26 Synthesis of (S_S)-*N*-[(*R*)-1-[(S_S)-*tert*-butylsulfinyl]-(2,4-diphenyl-3-pyrrolin-2-yl)]-*tert*-butanesulfinamide (S_S)-272

To a stirred solution of (S_S)-*N*-[2-bromo-1-phenylethylidene]-*tert*-butanesulfinamide (S_S)-**268a** (2 g, 6.62 mmol) in dry dichloromethane at -78 °C was added two equivalents of vinylmagnesium bromide

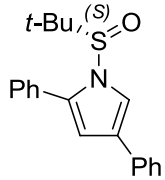
(1M solution in THF, 13.24 mL, 13.24 mmol) and the reaction mixture was allowed to stir for two hours at -78 °C, followed by four hours at -40 °C. The reaction mixture was quenched at this temperature by the addition of aq. NH_4Cl (5 mL) and extracted with dichloromethane (2 x 10 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated. The compound was isolated by means of column chromatography, followed by recrystallization from diethyl ether to afford (S_S)-*N*-[(*R*)-1-[(S_S)-*tert*-butylsulfinyl]-(2,4-diphenyl-3-pyrrolin-2-yl)]-*tert*-butanesulfinamide (S_S)-**272** (0.14 g) in 5% yield. Upon standing in the fridge for a longer period, the compound spontaneously transformed to (S_S)-1-(*tert*-butylsulfinyl)-2,4-diphenylpyrrole **278**.

(S_S)-*N*-[(*R*)-1-[(S_S)-*tert*-butylsulfinyl]-(2,4-diphenyl-3-pyrrolin-2-yl)]-*tert*-butanesulfinamide (S_S)-**272.** White crystals, yield 5%. Mp 130 ± 0.5 °C. $[\alpha]_D$ 13.4 (*c* 0.17, $CHCl_3$). IR (cm^{-1}): ν_{max} 696, 733, 760, 1041, 1085, 1453, 1604, 3238. ^1H NMR (300 MHz, $CDCl_3$): δ 1.08 (9H, s, *t*-Bu), 1.33 (9H, s, *t*-Bu), 4.02 (1H, dxd, *J* = 13.8 Hz, 2.2 Hz, C<u>H</u>(H)N), 4.35 (1H, s, NH), 4.96 (1H, dxd, *J* = 13.8 Hz, 1.7 Hz, CH(<u>H</u>)N), 6.73 (1H, dxd, *J* = 2.2 Hz, 1.7 Hz, CHC_q), 7.29-7.43 (6H, m, 6 x CH_{arom}), 7.48-7.59 (4H, m, 4 x CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.0 and 24.3 (2 x $C(\underline{C}H_3)_3$), 47.9 (CH_2N), 57.4 and 57.5 (2 x $\underline{C}(CH_3)_3$), 90.9 (C_qN), 125.9 ($\underline{C}HC_qN$), 126.3, 127.6, 128.3, 128.7, 128.8 and 129.0 (10 x CH_{arom}), 132.5, 138.9 and 140.7 (3 x C_q). MS (ES, pos. mode) *m/z* (%): 324 (M + H^+ - $NH_2S(O)$*t*-Bu, 100). Anal. Calcd for $C_{24}H_{32}N_2O_2S_2$: C 64.83; H 7.25; N 6.30. Found: C 64.34; H 7.36; N 6.25.



(S_S)-**272**

(S_S)-1-(*tert*-butylsulfinyl)-2,4-diphenylpyrrole 278. Colorless crystals. Mp 116 ± 0.5 °C. $[\alpha]_D$ -13.3 (*c* 0.23, $CHCl_3$). IR (cm^{-1}): ν_{max} 694, 760, 1028, 1042, 1066, 1084, 1102, 1452, 1602. ^1H NMR (300 MHz, $CDCl_3$): δ 1.06 (9H, s, *t*-Bu), 6.66 (1H, d, *J* = 1.9 Hz, C_qCHC_q), 7.33-7.44 (6H, m, 6 x CH_{arom}), 7.49-7.53 (2H, m, 2 x CH_{arom}), 7.56-7.60 (3H, m, 2 x CH_{arom} and CHN). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.6 ($C(\underline{C}H_3)_3$), 64.8 ($\underline{C}(CH_3)_3$), 110.1 ($C_q\underline{C}HC_q$), 115.0 (CHN), 125.3, 126.5, 126.9, 127.7, 128.5, 128.8 and 129.4 (10 x CH_{arom} and C_q), 131.9, 134.3 and 137.2 (3 x C_q). MS (ES, pos. mode) *m/z* (%): 324 (M + H^+, 100).



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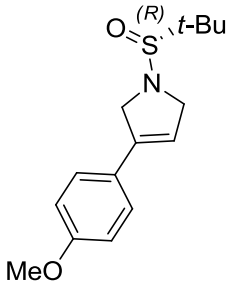
5.27 Synthesis of 3-aryl-*N*-(*tert*-butanesulfinyl)-3-pyrrolines 271

As a representative example, the synthesis of (R_S)-*N*-(*tert*-butanesulfinyl)-3-(4-methoxyphenyl)-3-pyrroline (R_S)-**271e** is described. (R_S)-*N*-[2-chloro-1-(4-methoxyphenyl)ethylidene]-*tert*-butanesulfinamide (R_S)-**282e** (0.67 g, 2.33 mmol) was dissolved in dry dichloromethane (20 mL) and the stirred solution was cooled to -78 °C. Two equiv of vinylmagnesium bromide (1M solution in THF, 4.66 mmol, 4.66 mL) were added to the solution and the reaction mixture was allowed to stir for two hours at -78 °C before prolongation at -40 °C for four hours. The reaction mixture was quenched at

this temperature by the addition of aq. NH_4Cl (5 mL) and immediately extracted with dichloromethane (2 x 10 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The compound was purified by means of recrystallization from diethyl ether to afford 0.44 g (1.57 mmol) (R_S)-*N*-(*tert*-butanesulfinyl)-3-(4-methoxyphenyl)-3-pyrroline (R_S)-**271e**.

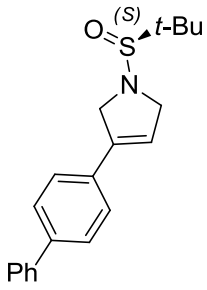
(R_S)-*N*-(*tert*-Butanesulfinyl)-3-(4-methoxyphenyl)-3-pyrroline (R_S)-271e. White crystals, yield 67%.



(R_S)-**271e**

Mp 89 ± 0.5 °C. $[\alpha]_D$ -26.3 (*c* 1.01, CH_2Cl_2). IR (cm^{-1}): ν_{max} 1114, 1367, 1512, 2936. ^1H NMR (300 MHz, $CDCl_3$): δ 1.50 (9H, s, *t*-Bu), 3.33-3.42 (1H, m, NC<u>H</u>(H)CH), 3.81 (3H, s, OMe), 3.81-3.88 (1H, m, NCH(<u>H</u>)CH), 4.25-4.32 (1H, m, C<u>H</u>(H)N), 4.37-4.46 (1H, m, CH(<u>H</u>)N), 5.92-5.96 (1H, m, C<u>H</u>CH_2), 6.85-6.90 and 7.26-7.31 (4H, 2 x m, 4 x CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.6 (C(<u>C</u>$H_3)_3$), 38.9 (N<u>C</u>H_2CH), 46.8 (CH_2N), 55.3 (OMe), 58.8 (<u>C</u>$(CH_3)_3$), 112.2 (<u>C</u>HCH_2N), 113.8 (2 x CH_{arom}), 126.7 (2 x CH_{arom}), 132.3 (C_{arom}), 139.9 (C_q), 159.4 (C_{arom}). MS (ES, pos. mode) *m/z* (%): 280.3 ($M + H^+$, 100).

(S_S)-*N*-(*tert*-Butanesulfinyl)-3-(4-phenylphenyl)-3-pyrroline (S_S)-271c. Brown crystals, yield 28%. Mp



(S_S)-**271c**

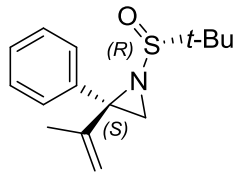
230 ± 0.5 °C. $[\alpha]_D$ 29.6 (*c* 0.1, DMF). IR (cm^{-1}): ν_{max} 765, 1102, 1195, 1479. ^1H NMR (300 MHz, $CDCl_3$): δ 1.51 (9H, s, *t*-Bu), 3.37-3.44 (1H, m, NC<u>H</u>(H)CH), 3.83-3.90 (1H, m, NCH(<u>H</u>)CH), 4.31-4.38 (1H, m, C<u>H</u>(H)N), 4.44-4.52 (1H, m, CH(<u>H</u>)N), 6.05-6.09 (1H, m, C<u>H</u>CH_2), 7.32-7.37 (1H, m, CH_{arom}), 7.40-7.46 and 7.56-7.61 (2 x 4H, 2 x m, 8 x CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.6 (C(<u>C</u>$H_3)_3$), 39.0 (N<u>C</u>H_2CH), 46.7 (CH_2N), 59.0 (<u>C</u>$(CH_3)_3$), 113.7 (<u>C</u>HCH_2N), 126.0, 127.0, 127.2, 127.4 and 128.8 (9 x CH_{arom}), 138.7, 140.1, 140.5 and 140.7 (3x C_{arom} and C_q). MS (ES, pos. mode) *m/z* (%): 326 ($M + H^+$, 100). HRMS (ES) calcd for $C_{20}H_{24}NOS^+$: 326.1573 MH^+; found: 326.1558.

5.28 Synthesis of (*Rs,S*)-1-(*tert*-butanesulfinyl)-2-isopropenyl-2-phenylaziridine 282

A solution of (R_S)-*N*-[2-chloro-1-phenylethylidene]-*tert*-butanesulfinamide (R_S)-**281a** (0.5 g, 1.94 mmol) in dry dichloromethane (10 mL) was cooled to -78 °C. 1.2 Equivalents of isopropenylmagnesium bromide (0.5M solution in THF, 4.66 mL, 2.33 mmol) was added and the reaction mixture was allowed to stir for two hours at -78 °C, followed by four hours at -40 °C. The reaction mixture was quenched at this temperature by the addition of aq. NH_4Cl (5 mL) and immediately extracted with dichloromethane (2 x 10 mL). The combined organic fractions were dried over $MgSO_4$, filtered and evaporated in vacuo. The compound was purified by means of column chromatography to afford (*Rs,S*)-1-(*tert*-butanesulfinyl)-2-isopropenyl-2-phenylaziridine **282** (0.35 g)

in 69% yield. When two equivalents of isopropenylmagnesium bromide were used, (R_S)-*N*-(3,5-dimethyl-2-phenylhexa-2,5-dien-1-yl)-2-*tert*-butanesulfinamide **283** was isolated in 17% yield next to (*Rs,S*)-1-(*tert*-butanesulfinyl)-2-isopropenyl-2-phenylaziridine **282** (33%).

(*Rs,S*)-1-(*tert*-butanesulfinyl)-2-isopropenyl-2-phenylaziridine 282. R_f = 0.28 (petroleum ether/EtOAc 3/1). Yellow crystals, yield 67%. Mp 54 ± 0.5 °C. $[\alpha]_D$ -394.7 (*c* 1.03, CH_2Cl_2). IR (cm^{-1}): ν_{max} 696, 1074, 1447, 2961. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 (9H, s, *t*-Bu), 1.65 (3H, s, CH_3), 2.11 (1H, s, C<u>H</u>$(H)_{azir}$), 3.23 (1H, s, CH(<u>H</u>)$_{azir}$), 4.95 (1H, s, C<u>H</u>(H)=C_q), 5.14 (1H, s, CH(<u>H</u>)=C_q), 7.26-7.47 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.8 (CH_3), 22.8 (C(<u>C</u>$H_3)_3$), 30.3 ($CH_{2,\ azir}$), 51.1 ($C_{q,\ azir}$), 57.4 (<u>C</u>$(CH_3)_3$), 112.9 (<u>C</u>H_2=Cq), 128.3 (2 x CH_{arom}), 128.5 (CH_{arom}), 129.7 (2 x CH_{arom}), 134.9 (C_{arom}), 145.4 (CH2=<u>C</u>q). MS (ES, pos. mode) *m/z* (%): 264.3 (M + H^+, 100).



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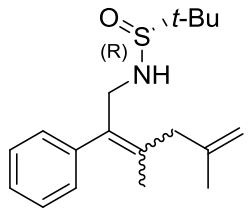
(R_S)-*N*-(3,5-dimethyl-2-phenylhexa-2,5-dien-1-yl)-2-*tert*-butanesulfinamide 283. R_f = 0.26 (petroleum ether/EtOAc 1/1). Yellow oil, yield 17%. IR (cm^{-1}): ν_{max} 730, 1052, 2958, 3212. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.09 (9H, s, *t*-Bu), 1.57 (3H, s, CH_3), 1.86 (3H, s, CH_3), 2.61 (2H, s, $C_qCH_2C_q$), 3.14 (1H, dxd, *J* = 7.2 Hz, 5.0 Hz, NH), 3.98 (1H, dxd, *J* = 13.2 Hz, 7.2 Hz, C<u>H</u>(H)NH), 4.15 (1H, dxd, *J* = 13.2 Hz, 5.0 Hz, CH(<u>H</u>)NH), 4.69 (1H, s, C<u>H</u>(H)=C_q), 4.77 (1H, s, CH(<u>H</u>)=C_q), 7.11-7.36 (5H, m, 5 x CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.6 (CH_3), 22.6 (CH_3 en C(<u>C</u>$H_3)_3$), 44.0 (C_q<u>C</u>H_2C_q), 47.9 (CH_2NH), 55.8 (<u>C</u>$(CH_3)_3$), 111.7 (<u>C</u>H_2=C_q), 126.7 (CH_{arom}), 128.2 (2 x CH_{arom}), 129.1 (2 x CH_{arom}), 133.9, 134.3, 141.3 and 143.8 (4 x C_q). MS (ES, pos. mode) *m/z* (%): 306.3 (M + H^+, 100).



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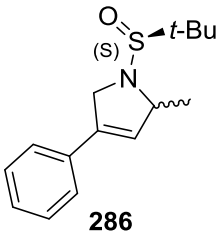
5.29 Synthesis of (S_S)-*N*-*tert*-butanesulfinyl 2-methyl-4-phenyl-3-pyrroline 286

(S_S)-*N*-[2-Chloro-1-ethylidene]-*tert*-butanesulfinamide (S_S)-**281a** (0.5 g, 1.94 mmol) was dissolved in dry dichloromethane (10 mL) and the stirred solution was cooled to -78 °C. Two equivalents of 2-propenylmagnesium bromide (0.5M solution in THF, 7.76 mL, 3.88 mmol) were added to the solution and the reaction mixture was allowed to stir for two hours at -78 °C before prolongation at -40 °C for four hours. The reaction mixture was quenched at this temperature by the addition of aq. NH_4Cl (5 mL) and immediately extracted with dichloromethane (2 x 10 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The compound was purified by column chromatography to afford (S_S)-*N*-*tert*-butanesulfinyl 2-methyl-4-phenyl-3-pyrroline **286** (0.07 g) in 13% yield as a 86:14 mixture of diastereomers.

Spectroscopic data of the major diastereomer obtained from the mixture of diastereomers **286** (dr 86:14).

(S_S)-*N*-*tert*-Butanesulfinyl 2-Methyl-4-phenyl-3-pyrroline 286. R_f = 0.24 (petroleum ether/EtOAc 3/1). Brown oil, yield 13%, dr 86:14. IR (cm^{-1}): ν_{max} 1114, 1367, 1512, 2936. ^1H NMR (300 MHz, $CDCl_3$): δ 1.51 (9H, s, *t*-Bu), 1.53 (3H, d, *J* = 6.6 Hz, CH_3), 3.88-3.98 (1H, m, C<u>H</u>CH_3), 4.20 (1H, dxdxd, *J* = 18.4 Hz, 3.0 Hz, 1.4 Hz, C<u>H</u>(H)N), 4.39 (1H, dxdxd, *J* = 18.4 Hz, 4.1 Hz, 1.9 Hz, CH(<u>H</u>)N), 5.70-5.72 (1H, m, C<u>H</u>CHN), 7.27-7.37 (5H, m, 5 x CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.2 (CH_3), 24.5 (C(<u>C</u>$H_3)_3$), 42.9 (CHN), 46.2 (CH_2N), 60.9 (<u>C</u>$(CH_3)_3$), 122.1 (<u>C</u>HCHN), 125.7 (2 x CH_{arom}), 127.9 (CH_{arom}), 128.6 (2 x CH_{arom}), 139.3 and 139.8 (2 x C_q). MS (ES, pos. mode) *m/z* (%): 264.3 (M + H^+, 100).



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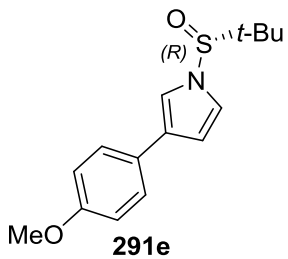
5.30 Synthesis of *N*-(*tert*-butanesulfinyl)-3-arylpyrroles 291

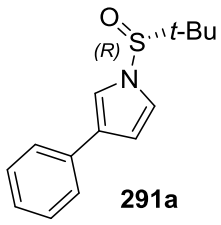
The synthesis of (R_S)-*N*-(*tert*-butanesulfinyl)-3-(4-methoxyphenyl)pyrrole **291e** is representative. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (0.9 equiv, 0.18 mmol, 42 mg) was dissolved in 1,4-dioxane (10 mL) and added dropwise to a solution of (R_S)-*N*-(*tert*-butanesulfinyl)-3-(4-methoxyphenyl)-3-pyrroline (R_S)-**271e** (57 mg, 0.20 mmol) in 1,4-dioxane (10 mL). After stirring for 16 hours at room temperature, the reaction mixture was quenched by the addition of a 10% solution of $NaHSO_3$ (5 mL) and immediately extracted with ethyl acetate (2 x 10 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The compound was purified by means of column chromatography to afford 49 mg (0.18 mmol) (R_S)-*N*-(*tert*-butanesulfinyl)-3-(4-methoxyphenyl)-pyrrole **291e**.

(R_S)-*N*-(*tert*-Butanesulfinyl)-3-(4-methoxyphenyl)pyrrole 291e. R_f = 0.29 (petroleum ether/EtOAc 3/1). Black crystals, yield 87%. Mp 134 ± 0.5 °C. $[\alpha]_D$ 28.7 (*c* 0.09, CH_2Cl_2). IR (cm^{-1}): ν_{max} 665, 823, 1187, 1273, 1591, 2928. ^1H NMR (300 MHz, $CDCl_3$): δ 1.45 (9H, s, *t*Bu), 3.82 (3H, s, OMe), 5.86 (1H, dxd, *J* = 9.9 Hz, 1.7 Hz, C<u>H</u>CHN), 6.89-6.93 (2H, m, 2 x CH_{arom}), 7.22-7.26 (2H, m, 2 x CH_{arom}), 7.53 (1H, dxd, *J* = 9.9 Hz, 2.2 Hz, CHC<u>H</u>N), 7.68-7.70 (1H, m, CCHN). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.2 (C(<u>C</u>$H_3)_3$), 55.4 (OMe), 62.1 (<u>C</u>$(CH_3)_3$), 88.8 (<u>C</u>HCHN), 113.8 (C_q), 114.3 (2 x CH_{arom}), 126.6 (2 x CH_{arom}), 131.4 (C_q), 139.8 (N<u>C</u>HCH), 144.9 (CH), 158.2 (C_q). MS (ES, pos. mode) *m/z* (%): 278.3 (M + H^+, 100).



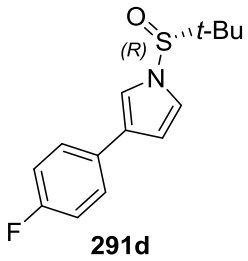
291e

(R_S)-*N*-(*tert*-Butanesulfinyl)-3-phenylpyrrole 291a. R_f = 0.22 (petroleum ether/EtOAc 3/1). Green crystals, yield 71%. Mp 126 ± 0.5 °C. $[\alpha]_D$ 51.6 (*c* 0.1, CH_2Cl_2). IR (cm^{-1}): ν_{max} 698, 820, 1174, 1335, 1591, 2923. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.46 (9H, s, *t*-Bu), 5.88 (1H, dxd, *J* = 9.9 Hz, 1.1 Hz, C<u>H</u>CHN), 7.21-7.26 (1H, m, CH_{arom}), 7.31-7.39 (4H, m, CH_{arom}), 7.59 (1H, dxd, *J* = 9.9 Hz, 2.2 Hz, CHC<u>H</u>N), 7.76-7.79 (1H, m, CHN). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.2 (C(<u>C</u>H_3)$_3$), 62.2 (<u>C</u>(CH_3)$_3$), 89.0 (<u>C</u>HCHN), 114.0 (C_q), 125.4 (2 x CH_{arom}), 126.1 (CH_{arom}), 128.9 (2 x CH_{arom}), 138.8 (C_q), 139.8 (N<u>C</u>HCH), 145.8 (CH). MS (ES, pos. mode) *m/z* (%): 248.3 (M + H^+, 100). Anal. Calcd for $C_{14}H_{17}NOS$: C 67.98; H 6.93; N 5.66. Found: C 67.84; H 6.89; N 5.21.



291a

(R_S)-*N*-(*tert*-Butanesulfinyl)-3-(4-fluorophenyl)pyrrole 291d. R_f = 0.29 (petroleum ether/EtOAc 3/1). Green crystals, yield 69%. Mp 114 ± 0.5 °C. $[\alpha]_D$ 28.2 (*c* 0.1, $CHCl_3$). IR (cm^{-1}): ν_{max} 662, 731, 762, 806, 1167, 1277, 1455, 1510, 1588, 1598. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.46 (9H, s, *t*-Bu), 5.88 (1H, dxd, *J* = 10.0 Hz, 1.4 Hz, C<u>H</u>CHN), 7.01-7.07 (2H, m, 2 x CH_{arom}), 7.23-7.28 (2H, m, 2 x CH_{arom}), 7.52 (1H, dxd, *J* = 10.0 Hz, 2.5 Hz, CHC<u>H</u>N), 7.70 (1H, dxd, *J* = 2.5 Hz, 1.4 Hz, CCHN). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.2 (C(<u>C</u>H_3)$_3$), 62.2 (<u>C</u>(CH_3)$_3$), 89.1 (<u>C</u>HCHN), 113.3 (C_q), 115.7 (d, *J* = 20.8 Hz, 2 x CH_{arom}), 127.0 (d, *J* = 8.1 Hz, 2 x CH_{arom}), 134.9 (d, *J* = 3.5 Hz, C_{arom}), 139.7 (N<u>C</u>HCH), 145.5 (CH), 161.7 (d, *J* = 244.6 Hz, $C_{q,\ F,\ arom}$). MS (ES, pos. mode) *m/z* (%): 266 (M + H^+, 100). HRMS (ES) calcd for $C_{14}H_{17}FNOS^+$: 266.1009 MH^+; found: 266.1011.

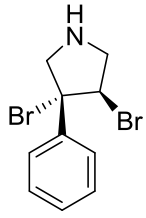


291d

5.31 Synthesis of 3,4-dibromo-3-phenylpyrrolidine 292

A solution of (R_S)-*N*-(*tert*-butanesulfinyl)-3-phenyl-3-pyrroline (R_S)-**271e** (0.1 g, 0.40 mmol) in dry CH_2Cl_2 (10 mL) was cooled to 0 °C and Br_2 (1.05 equiv, 0.42 mmol, 0.023 mL) was added dropwise. After stirring for 1 h, Et_3N (1 equiv, 0.06 mL, 0.40 mmol) was added, and the reaction mixture was allowed to stir for another 30 minutes at room temperature. Water (10 mL) was added, and the reaction mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated in vacuo. The compound was purified by means of column chromatography to afford 0.04 g (0.13 mmol) 3,4-dibromo-3-phenylpyrrolidine **292**.

3,4-dibromo-3-phenylpyrrolidine 292. R_f = 0.18 (petroleum ether/EtOAc 3/1). brown oil, yield 33%. IR (cm^{-1}): ν_{max} 1156, 1337, 2359, 3271. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.73 (1H, dxd, *J* = 15.0 Hz, 3.3 Hz, C<u>H</u>(H)NH), 3.91-3.99 (1H, m, C_qC<u>H</u>(H)NH), 4.35 (1H, dxd, *J* = 15.0 Hz, 4.1 Hz, CH(<u>H</u>)NH), 4.62 (1H, dxd, *J* = 15.4 Hz, 11.6 Hz, C_qCH(<u>H</u>)NH), 5.11-5.23 (2H, m, NH en CHBr), 7.38-7.48 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 49.9 (C_qCH_2N), 50.8 (CHBr), 53.0 (CH_2N), 66.3 (C_q), 126.2 (2 x CH_{arom}), 129.1 (2 x CH_{arom}), 129.6 (CH_{arom}), 140.0 (C_{arom}). MS (ES, pos. mode) *m/z* (%): inconclusive MS.



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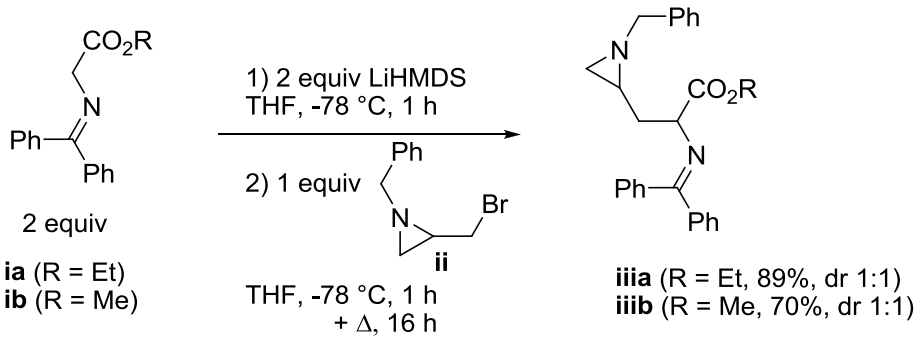
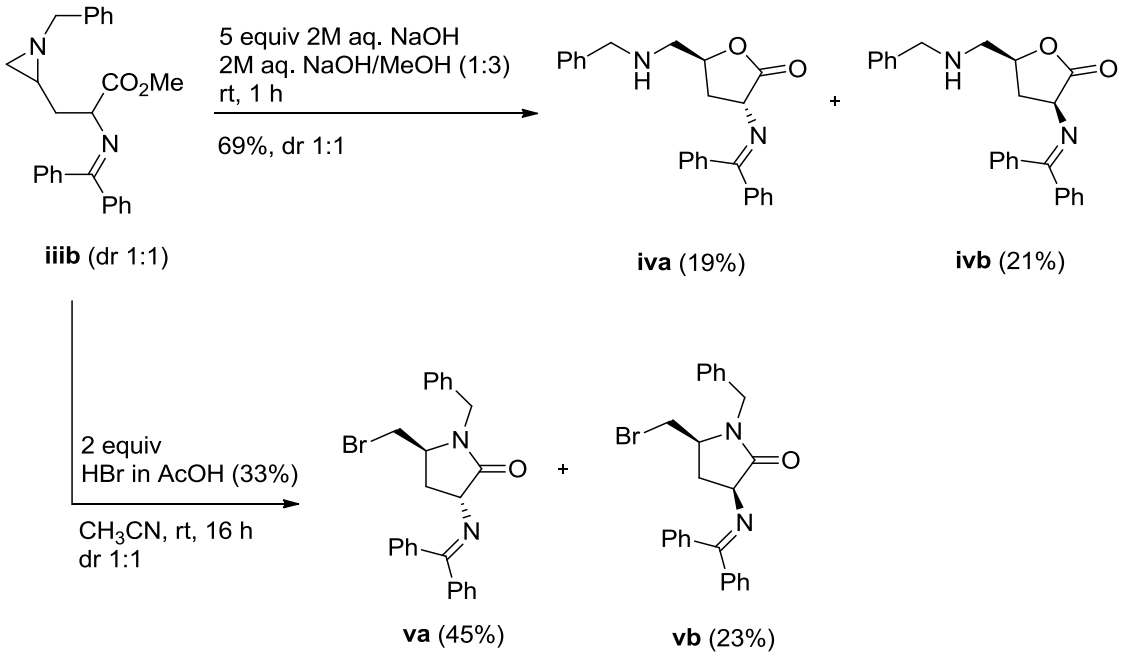
6 Summary

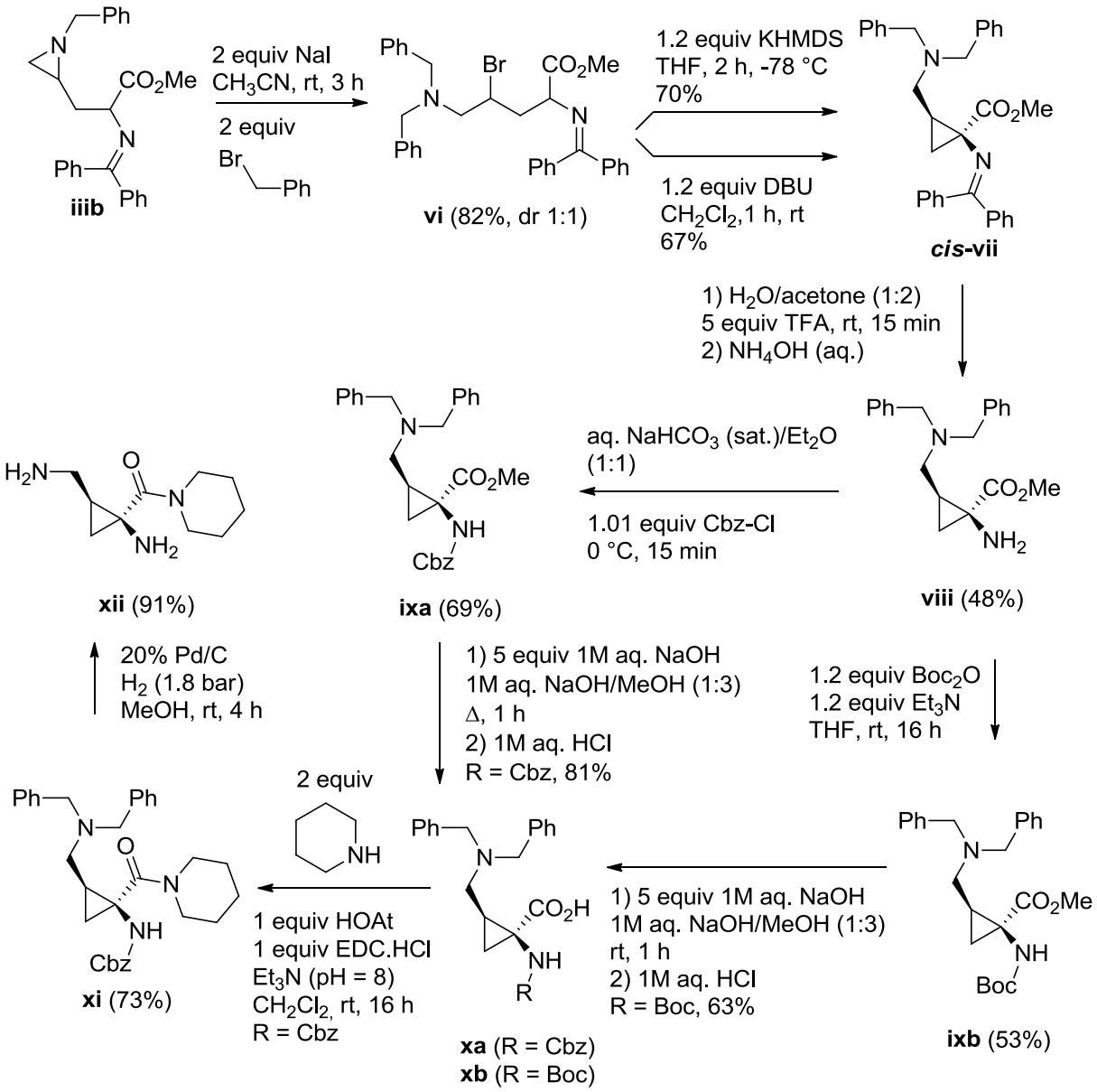
Aziridines, nitrogen-containing three-membered ring heterocycles, are well established useful and versatile building blocks in organic synthesis and medicinal chemistry. Next to the fact that some naturally occurring compounds, bearing the aziridine functionality, show interesting biological activity, the presence of the highly strained ring system makes these heterocycles very useful building blocks for chemical bond elaborations and functional group transformations to a variety of nitrogen-containing compounds. In that respect, the synthesis of new classes of functionalized aziridines, as building blocks for novel nitrogen-containing acyclic, heterocyclic or carbocyclic coumpounds, was pursued within this PhD-thesis. In a first approach, substitution of 2-(bromomethyl)aziridine **ii** with protected glycine esters **i** afforded γ,δ-aziridino α-amino acid derivatives **iii** as a 1:1 mixture of diastereomers in good yield.



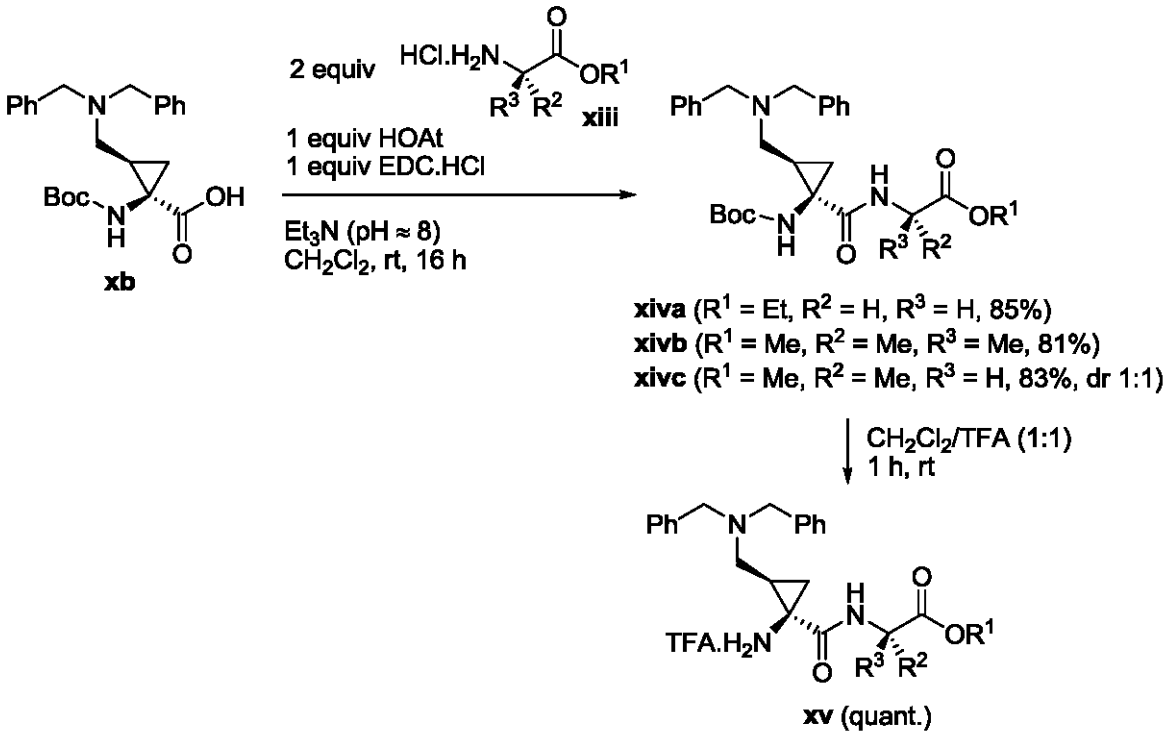
To date, only one other synthesis resulting in γ,δ-aziridino α-amino acid derivatives in low yield has been described in literature (see section 2.2.1)[37b] and the reactivity of this relatively new class of conformationally constrained α,γ-diamino acid derivatives was further investigated. Saponification of the ester function, present in aziridine **iiib**, with NaOH resulted in a ring transformation of the obtained carboxylate to the corresponding lactones **iv**, while treatment with hydrobromic acid resulted in ring opening at the unsubstituted carbon atom of the aziridine moiety, followed by intramolecular ring closure to the corresponding lactams **v**. Both lactams **v** and lactones **iv** were obtained as a mixture of diastereomers in a 1:1 diastereomeric ratio and were separated from each other by means of column chromatography.

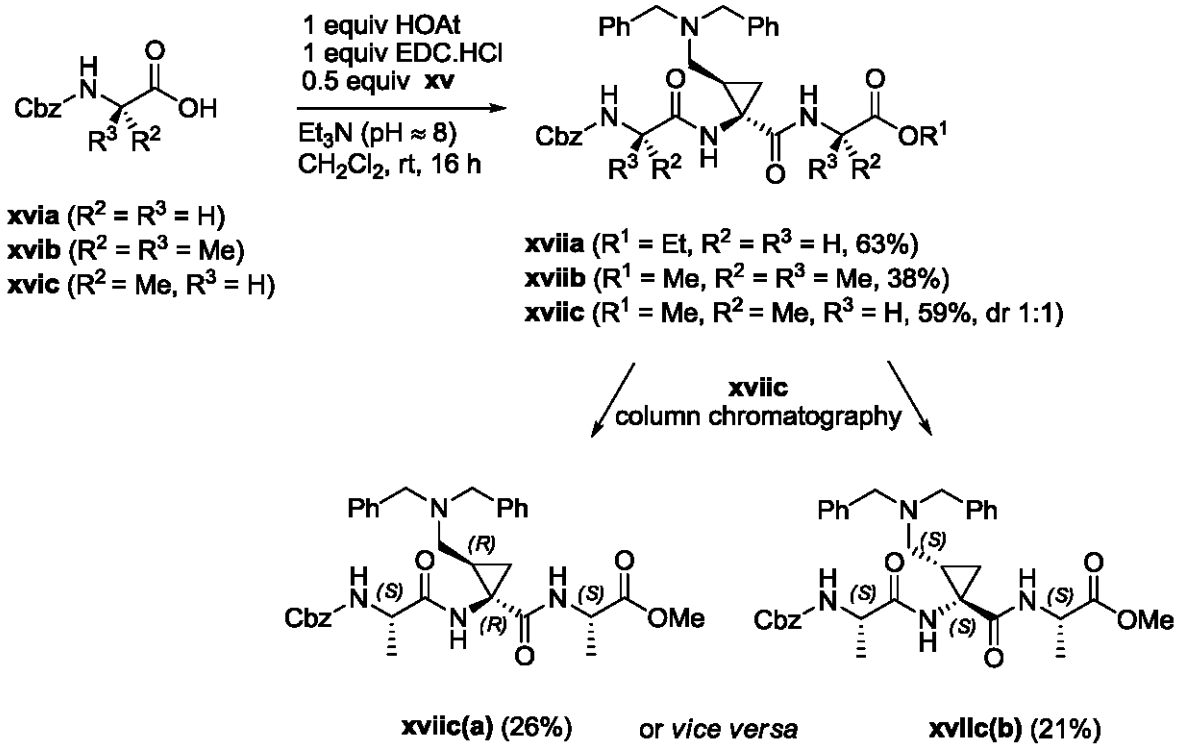


As aziridines already showed their potential as precursors in cyclopropane synthesis, the utility of aziridine **iiib** as substrate for ring transformation to the corresponding cyclopropane derivatives was further investigated. Ring opening with benzyl bromide at the more hindered carbon atom of the aziridine **iiib** resulted in the formation of β-bromoamine **vi** as a 1:1 mixture of diastereomers. Subsequent deprotonation with KHMDS or DBU at the α-position of the ester moiety, followed by bromide expulsion gave ring closure to *cis*-cyclopropane ***cis*-vii** with excellent diastereoselectivity (dr 98:2). To allow saponification of the ester function, other appropriate *N*-protecting groups were introduced. The *N*-diphenylmethylidene group of cyclopropane ***cis*-vii** was removed with TFA and the free amine **viii** was reprotected upon reaction with Cbz-Cl or Boc_2O to give *N*-Cbz or *N*-Boc-protected cyclopropanes **ix**. Saponification of the latter compounds was possible and subsequent coupling of the resulting carboxylic acid **xa** with piperidine resulted in the formation of amide **xi**. Deprotection of the amino functions led to the formation of a new 2,3-methano analogue **xii** of *N*-[(*S*)-2,4-diaminobutanoyl]piperidine as a possible conformationally constrained inhibitor of the enzyme DPPII.



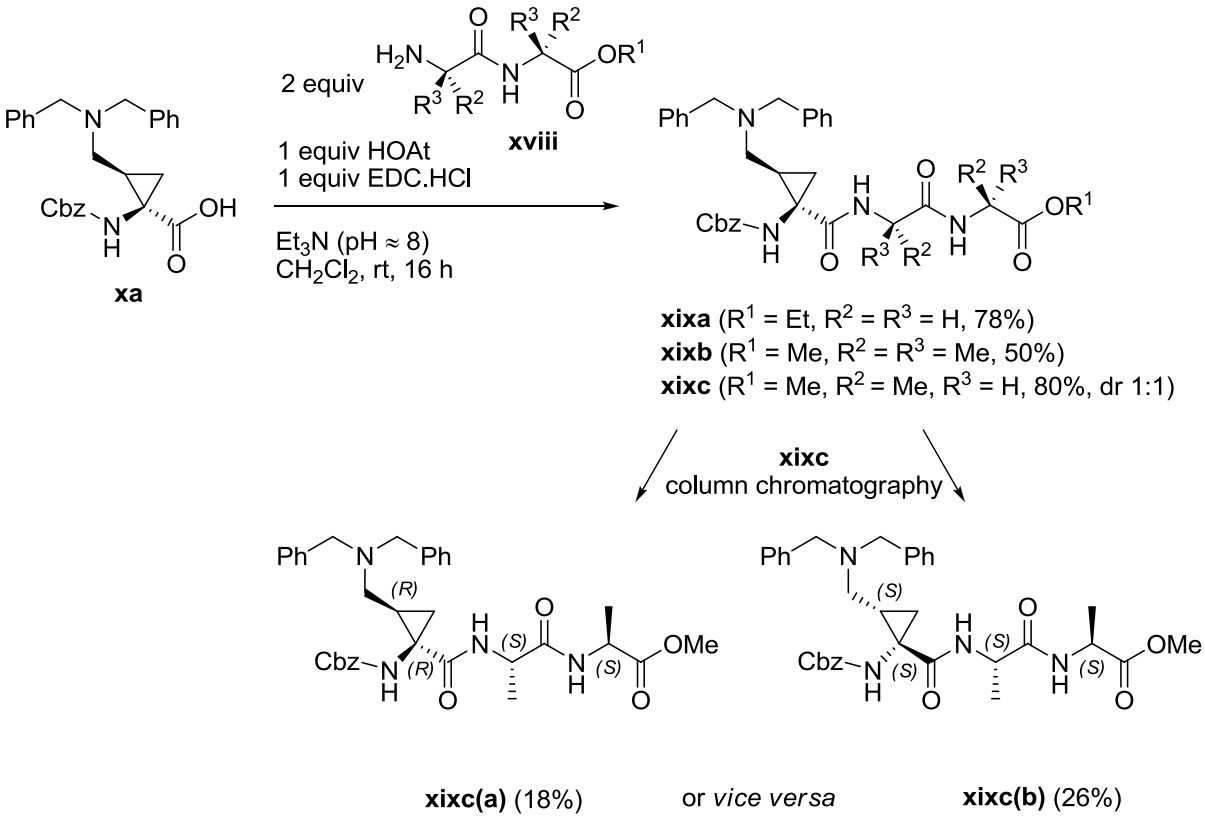
The use of conformationally constrained C^{α}-tetrasubstituted amino acids has gained a lot of attention in the field of foldamers in recent years. In this respect, the synthesized 2-aminomethyl-substituted 1-aminocyclopropane-1-carboxylic acids (ACC) **x** were used in the synthesis of selected tripeptides to study their preferential conformations. Boc-protected carboxylic acid **xb** was coupled with amino esters **xiii** to the corresponding dipeptides **xiv** and subsequent removal of the Boc-protecting group led to TFA-salts **xv**. In the next step, the obtained salts were coupled with carboxylic acids **xvi** to the desired tripeptides **xvii**. In the case of peptides containing alanine (**xvic**), a 1:1 mixture of diastereomers was obtained, which were separated *via* column chromatography to yield **xviic(a)** and **xviic(b)** as pure compounds in 26% and 21% yield, respectively.



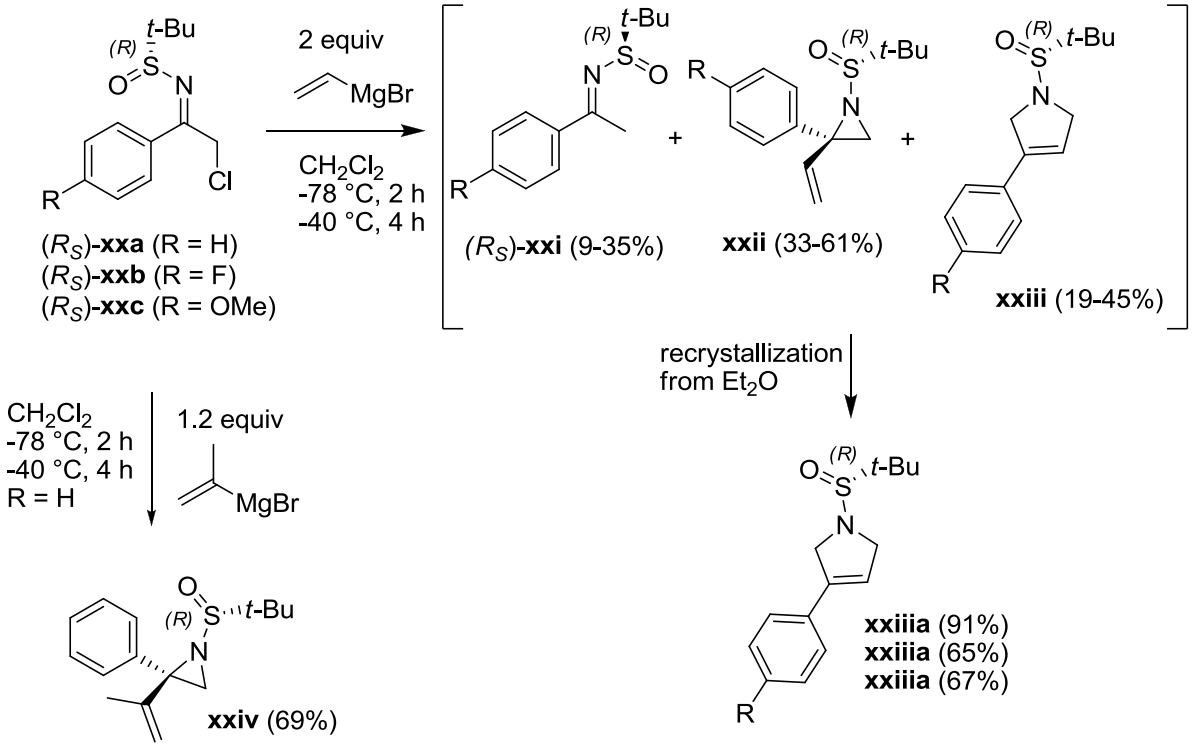


Tripeptides containing the 2-aminomethyl-ACC derivative at the *N*-terminus were also synthesized and therefore *N*-Cbz-protected carboxylic acid **xa** was coupled with dipeptides **xviii** to the corresponding tripeptides **xix** in 50-80% yield. Again both diastereomers of the tripeptide **xixc**

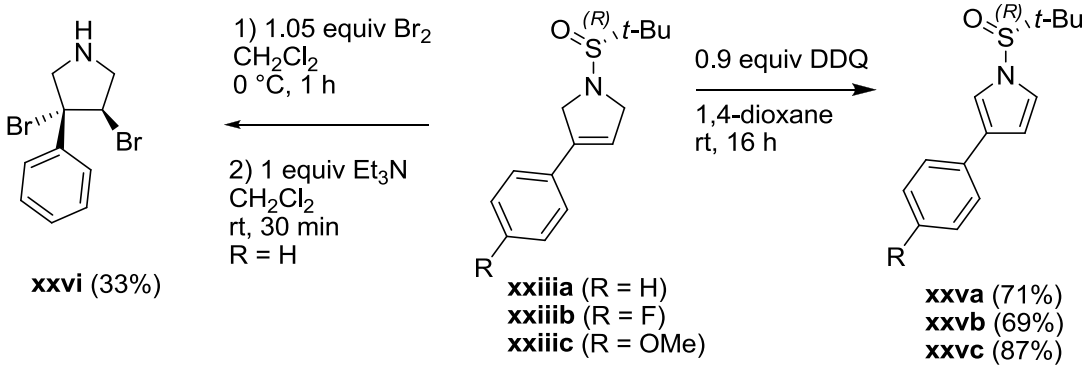
containing alanine were separated *via* column chromatography to give **xixc(a)** and **xixc(b)** as optically active compounds.



In a second part, the synthesis of unreported chiral *N*-sulfinyl 2-aryl-2-alkenylaziridines was envisioned *via* addition of alkenylmagnesium bromides across aromatic *N*-sulfinyl α-haloketimines. Analysis of the crude reaction mixtures after reaction of α-chloroketimines (R_S)-**xx** with vinylmagnesium bromide revealed the presence of both 2-vinylaziridines **xxii** and 3-pyrrolines **xxiii**, next to dehalogenated starting materials **xxi**. Upon recrystallization of the crude reaction mixtures, however, aziridines **xxii** spontaneously rearranged to the corresponding 3-aryl-3-pyrrolines **xxiii**, which were isolated in 65-91% yield.

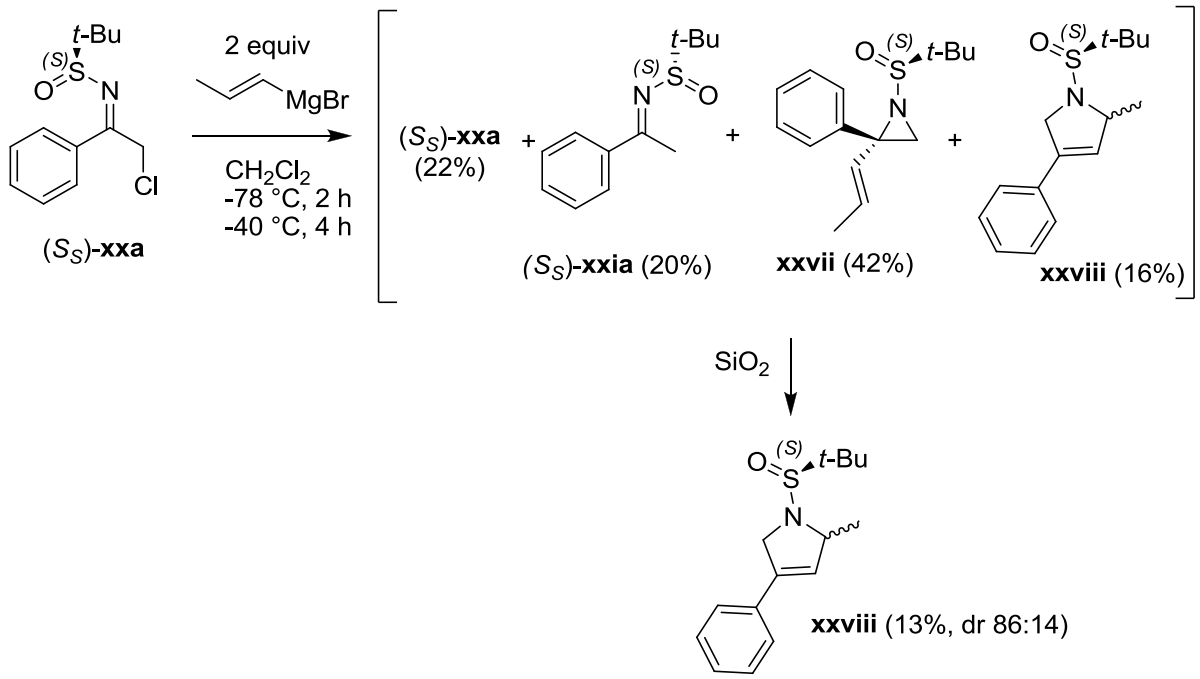


To confirm their structural identity, pyrrolines **xxiii** were oxidized to the corresponding pyrroles **xxv** in the presence of DDQ, while reaction with Br_2 afforded 3,4-dibromopyrrolidine **xxvi** in moderate yield with spontaneous cleavage of the protective group at nitrogen.



To extend the scope of this reaction, reaction of α-chloroketimine (R_S)-**xxa** with isopropenylmagnesium bromide was investigated. This time, formation of 3-aryl-3-pyrroline was not observed and 2-isopropenylaziridine **xxiv** was isolated as a stable compound in 69% yield. The sluggish reaction of α-chloroketimine (S_S)-**xxa** with 1-propenylmagnesium bromide further indicates that the rate of rearrangement of 2-alkenylaziridines is influenced by subtle steric effects exerted by the substituents on the double bond. Next to a significant amount of unreacted and dehalogenated starting material (S_S)-**xxa** and (S_S)-**xxia**, both aziridine **xxvii** and 3-pyrroline **xxviii** were present in the

crude reaction mixture. However, after purification only 3-pyrroline **xxviii** was isolated in low yield (13%, dr 86:14).



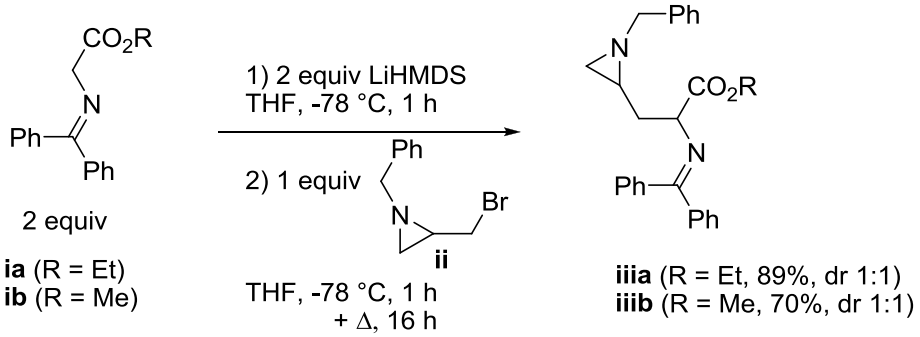
In conclusion, the synthesized 2-(carboxyethyl)aziridines proved to be a valuable addition to the arsenal of functionalized aziridines as synthetic building blocks, since the high synthetic potential of these 2-(carboxyethyl)aziridines was further demonstrated by means of their elaboration into different types of heterocyclic and carbocyclic compounds, including γ-lactones, γ-lactams and cyclopropanes.

The synthesized 2-aminomethyl-substituted 1-aminocyclopropane-1-carboxylic acid derivatives proved to be excellent precursors for the synthesis of a new conformationally constrained analogue of (*S*)-2,4-diaminobutanoylpiperidine (Dab-Pip) and were used as alternative α-amino acids in small peptides to study their conformational preferences.

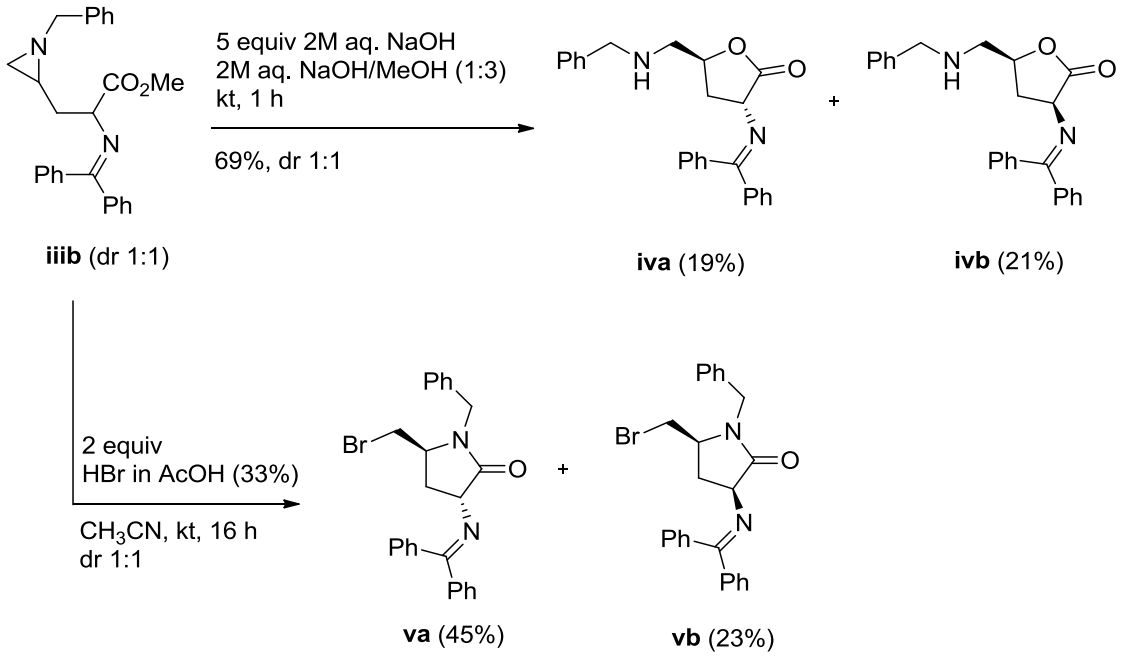
Finally, chiral *N*-(*tert*-butanesulfinyl)-3-pyrrolines and -2-(isopropenyl)aziridine were obtained *via* a straightforward synthesis starting from aromatic *N*-sulfinyl α-chloroketimines.

7 Samenvatting

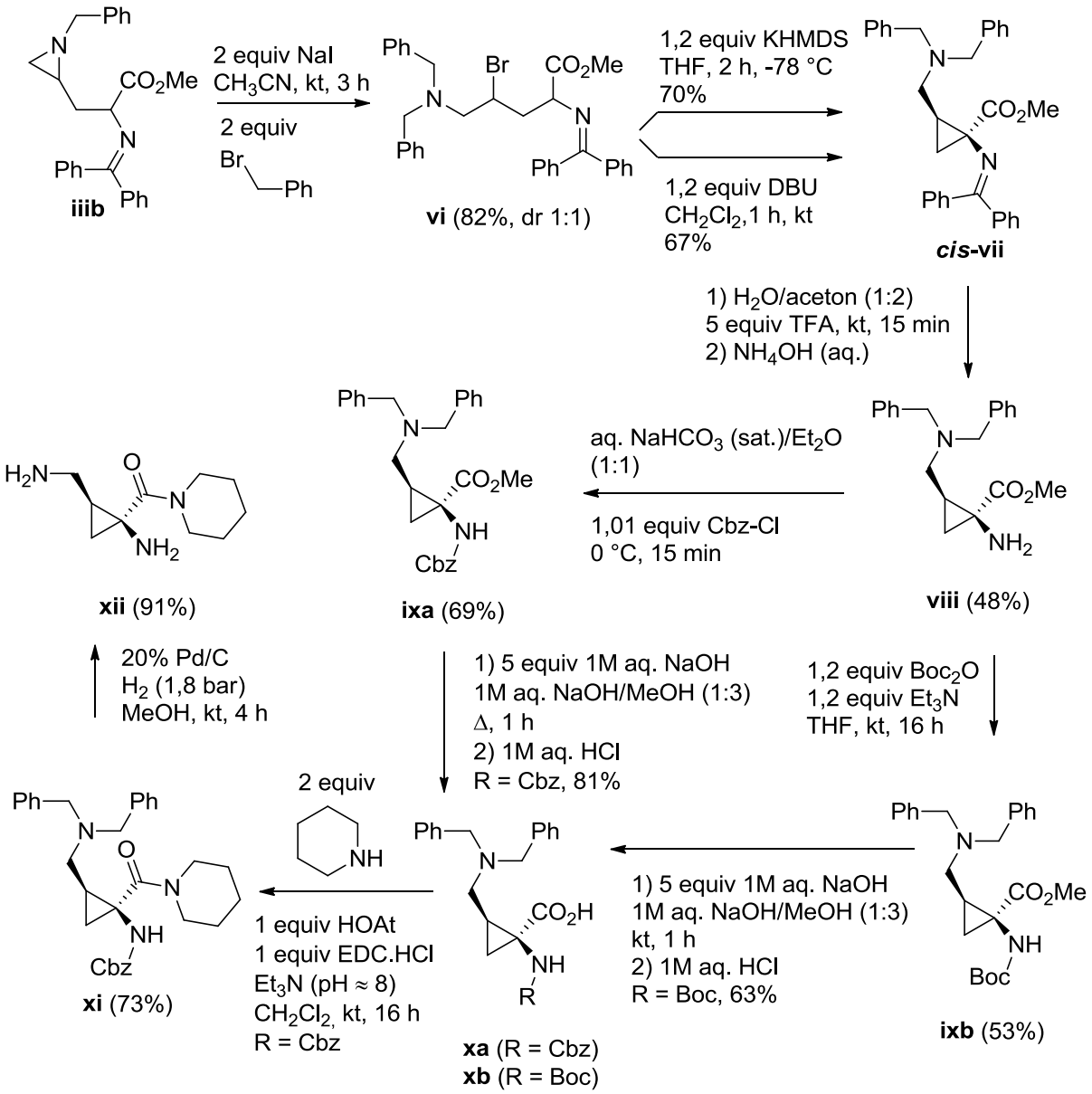
Aziridinen, stikstofbevattende drieringstructuren, zijn bruikbare en veelzijdige bouwstenen in de organische synthese en medicinale chemie. Naast het feit dat sommige natuurproducten, die de aziridine functionaliteit bevatten, interessante biologische activiteit vertonen, maakt de aanwezigheid van de gespannen driering deze heterocyclische verbindingen tot geschikte bouwstenen voor de verdere omzetting naar een waaier van stikstofhoudende verbindingen. In dit opzicht werd de synthese van nieuwe klassen van gefunctionaliseerde aziridinen, als bouwsteen voor nieuwe stikstofbevattende acyclische, heterocyclische en carbocyclische verbindingen, nagestreefd binnen dit doctoraatsonderzoek. In een eerste luik gaf de substitutie van 2-(broommethyl)aziridine **ii** met beschermde glycine esters **i** aanleiding tot de vorming van γ,δ-aziridino α-aminozuurderivativen **iii** in een 1:1 mengsel van diastereomeren in goed rendement.



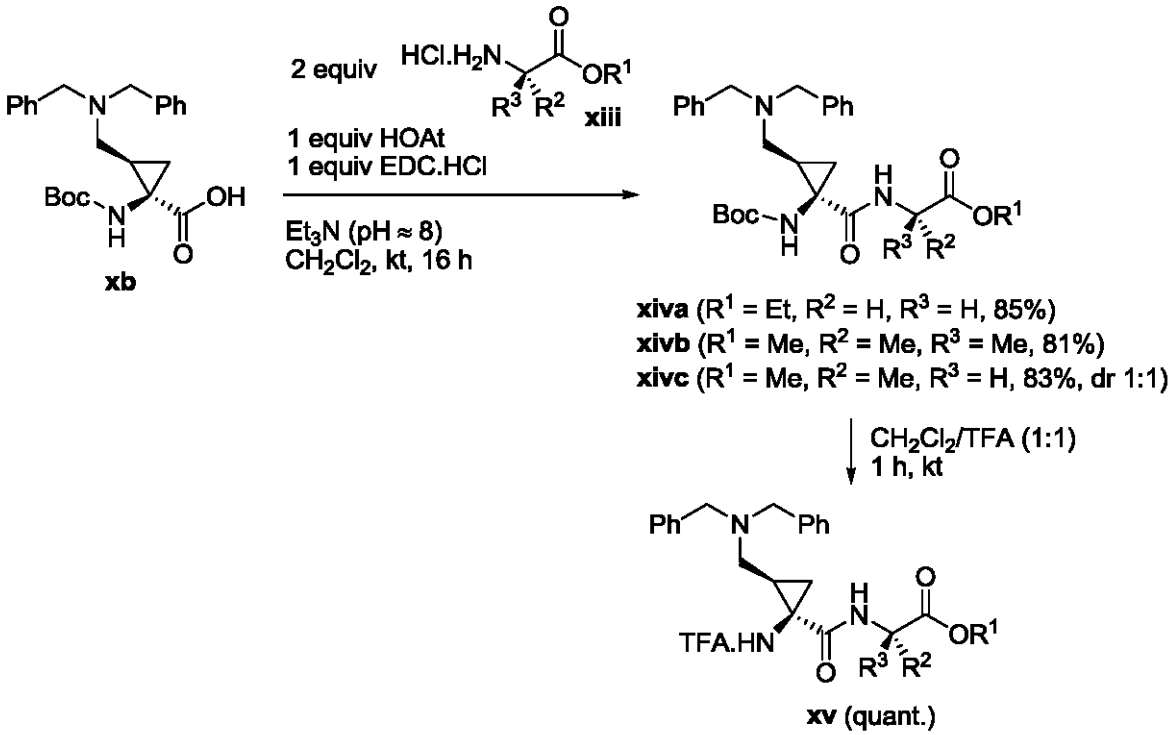
Tot op heden is slechts één andere synthese in de literatuur beschreven die aanleiding geeft tot γ,δ-aziridino α-aminozuurderivativen in laag rendement (zie sectie 2.2.1)[37b] en de reactiviteit van deze relatief nieuwe klasse van conformationeel beperkte α,γ-diaminozuurderivaten werd verder onderzocht. Verzeping van de esterfunctie aanwezig in aziridine **iiib** met NaOH leidde tot een ringtransformatie van het gevormde carboxylaat tot de overeenkomstige lactonen **iv**, terwijl behandeling met waterstofbromide resulteerde in ringopening aan het niet-gesubstitueerde koolstofatoom van de aziridine groep, gevolgd door intramoleculaire ringsluiting naar de overeenkomstige lactamen **v**. Zowel lactamen **v** als lactonen **iv** werden gevormd als een mengsel van diastereomeren in een 1:1 diastereomere verhouding en konden van elkaar gescheiden worden *via* kolomchromatografie.

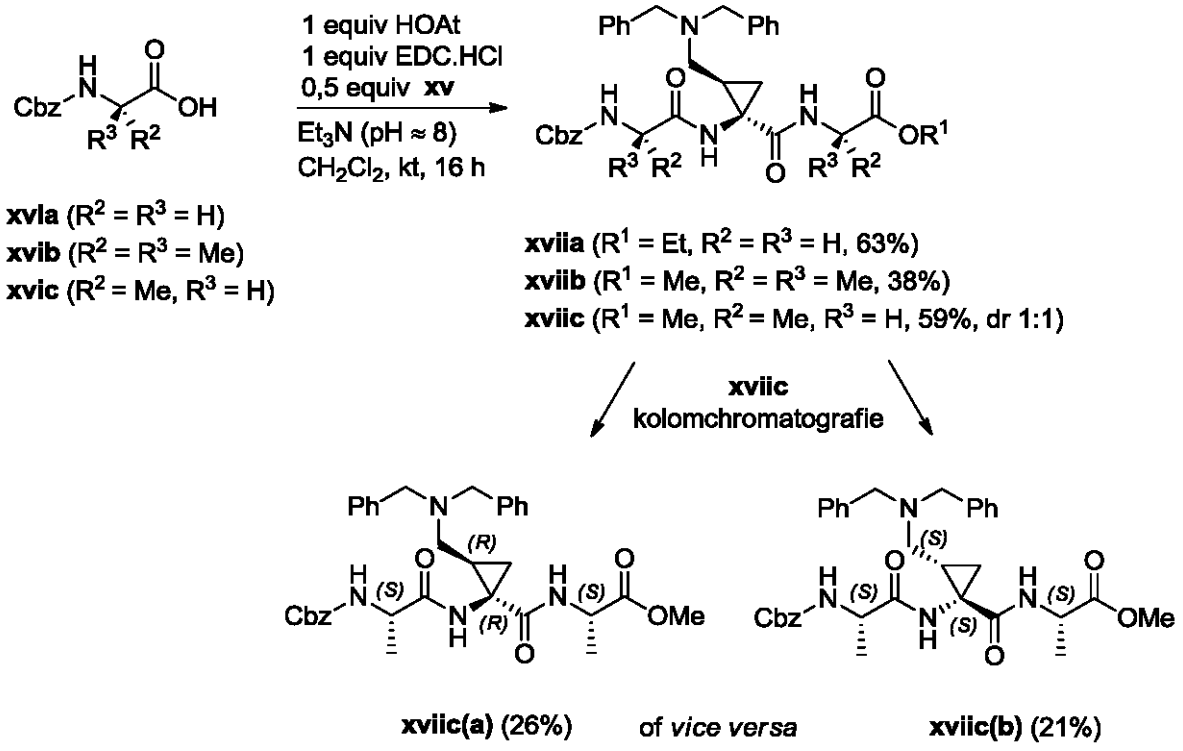


Gezien aziridinen hun potentieel als precursor in de synthese van cyclopropanen reeds hebben bewezen, werd het gebruik van aziridine **iiib** als substraat voor ringtransformatie tot de overeenkomstige cyclopropaanderivaten verder onderzocht. Ringopening met benzylbromide aan het meer gehinderde koolstofatoom van aziridine **iiib** gaf aanleiding tot de vorming van β-broomamine **vi** als een 1:1 mengsel van diastereomeren. Deprotonering met KHMDS of DBU van de α-positie van de estergroep, gevolgd door uitstoot van bromide gaf ringsluiting tot *cis*-cyclopropaan ***cis*-vii** met uitstekende diastereoselectiviteit (dr 98:2). Om verzeping van de esterfunctie mogelijk te maken dienden andere geschikte *N*-beschermende groepen geïntroduceerd te worden. De *N*-difenylmethylideengroep van cyclopropaan ***cis*-vii** werd verwijderd met TFA en het vrije amine **viii** werd opnieuw beschermd *via* reactie met Cbz-Cl of Boc_2O en gaf aanleiding tot *N*-Cbz of *N*-Boc-beschermde cyclopropanen **ix**. Verzeping van de laatstgenoemde verbindingen was mogelijk en daaropvolgende koppeling van het bekomen carbonzuur **xa** met piperidine leidde tot de vorming van amide **xi**. Ontscherming van de aminofunctionaliteiten gaf aanleiding tot een nieuw 2,3-methanoanaloog **xii** van *N*-[(*S*)-2,4-diaminobutanoyl]piperidine als een potentiële conformationeel beperkte inhibitor van het enzym DPPII.



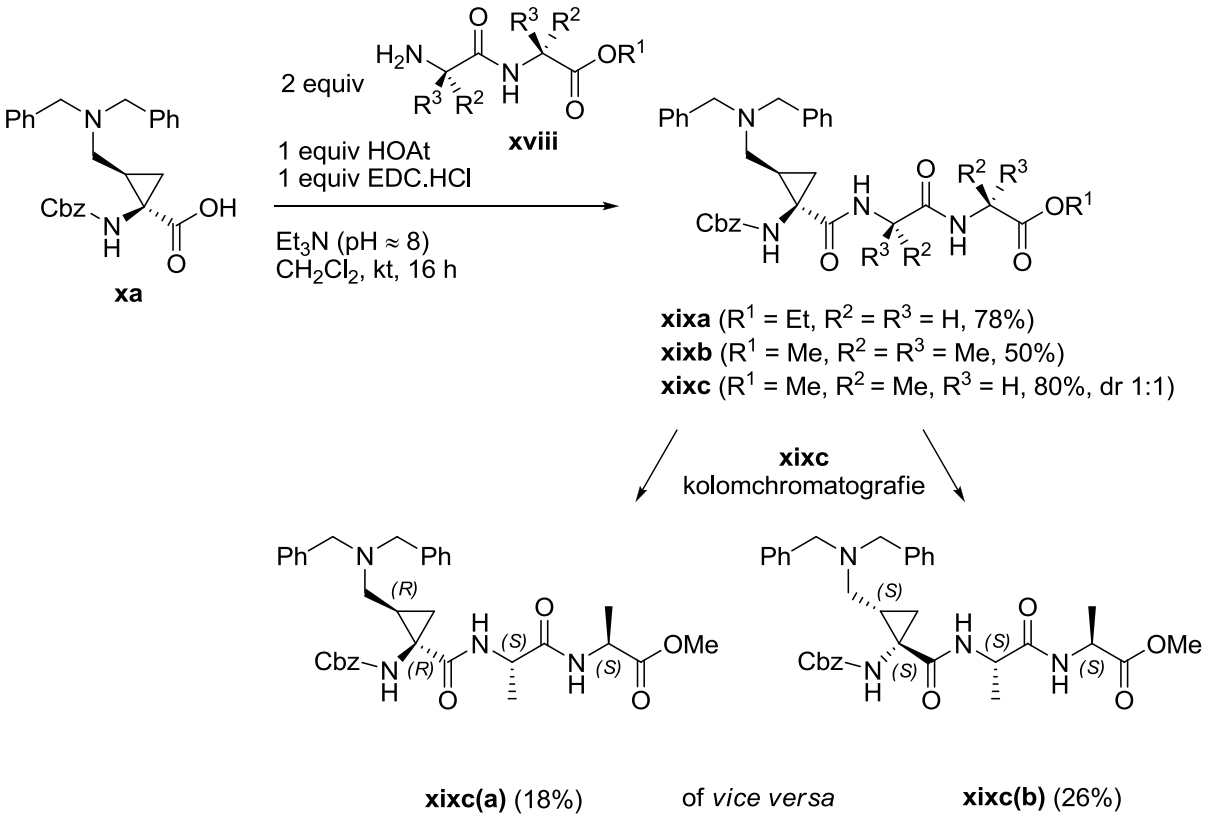
Het gebruik van conformationeel beperkte C^{α}-tetragesubstitueerde aminozuren heeft de laatste jaren aan belang gewonnen binnen het domein van de foldameren. In dit opzicht werden de gesynthetiseerde 2-aminomethyl-gesubstitueerde 1-aminocyclopropaan-1-carbonzuren (ACC) **x** gebruikt in de synthese van geselecteerde tripeptiden om hun preferentiële conformaties te onderzoeken. Boc-beschermd carbonzuur **xb** werd gekoppeld met aminoesters **xiii** tot de overeenkomstige dipeptiden **xiv** en daaropvolgende verwijdering van de Boc-beschermende groep leidde tot TFA-zouten **xv**. In een volgende stap werden de verkregen zouten gekoppeld met carbonzuren **xvi** tot de gewenste tripeptiden **xvii**. In het geval van de alanine-bevattende peptiden (**xvic**) werd een 1:1 mengsel van diastereomeren verkregen, die van elkaar gescheiden werden *via* kolomchromatografie om **xviic(a)** en **xviic(b)** te bekomen in 26% en 21% rendement, respectievelijk.



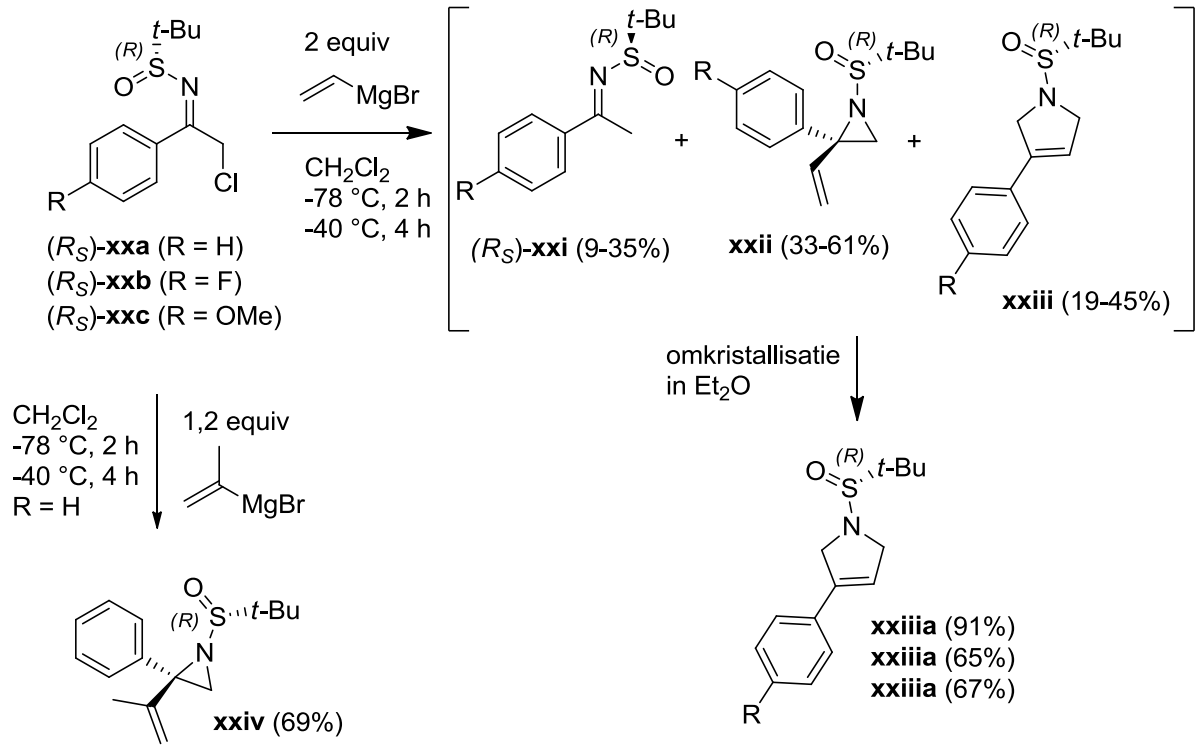


Tripeptiden met het 2-aminomethyl-ACC derivaat aan de *N*-terminus werden ook gesynthetiseerd en daartoe werd *N*-Cbz-beschermd carbonzuur **xa** gekoppeld met dipeptiden **xviii** tot de overeenkomstige tripeptiden **xix** in 50-80% rendement. Opnieuw konden beide diastereomeren van

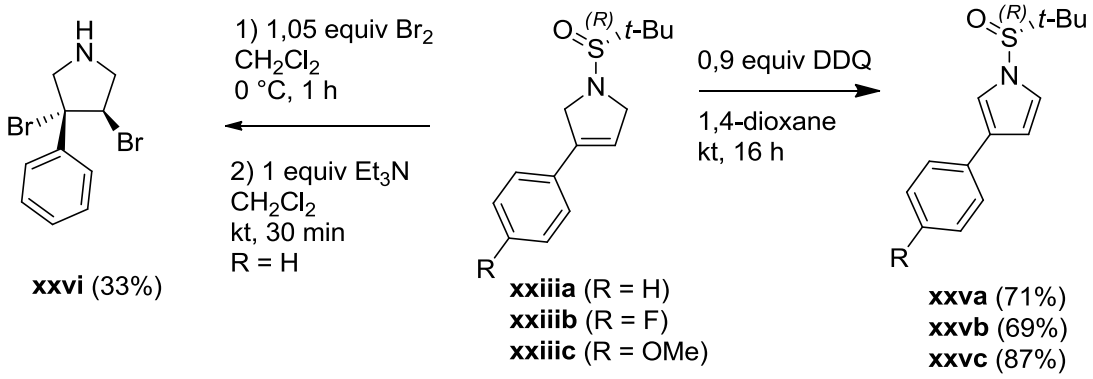
het alanine-houdende tripeptide **xixc** gescheiden worden *via* kolomchromatografie tot **xixc(a)** and **xixc(b)** als optisch actieve verbindingen.



In een tweede luik werd de synthese van ongerapporteerde chirale *N*-sulfinyl 2-aryl-2-alkenylaziridinen vooropgesteld *via* additie van alkenylmagnesium bromiden aan aromatische *N*-sulfinyl α-haloketiminen. Analyse van de ruwe reactiemengsels na reactie van α-chloorketiminen (R_S)-**xx** met vinylmagnesium bromide toonde de aanwezigheid aan van 2-vinylaziridinen **xxii** en 3-pyrrolinen **xxiii**, naast gedehalogeneerd uitgangsproduct **xxi**. Tijdens omkristallisatie van de ruwe reactiemengsels vond echter een spontane omlegging van aziridinen **xxii** plaats tot de overeenkomstige 3-aryl-3-pyrrolinen **xxiii**, die geïsoleerd konden worden in 65-91% rendement.

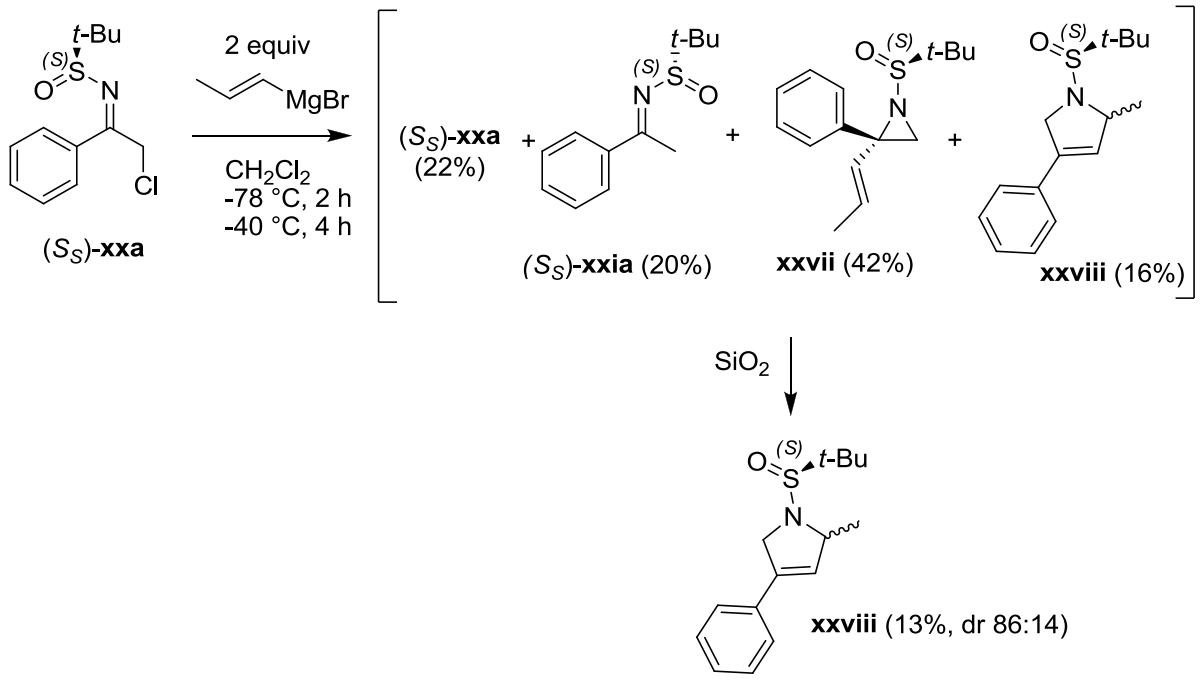


Om hun structurele identiteit te bevestigen werden pyrrolinen **xxiii** geoxideerd tot de overeenkomstige pyrrolen **xxv** in de aanwezigheid van DDQ, terwijl reactie met Br_2 aanleiding gaf tot de vorming van 3,4-dibroompyrrolidine **xxvi** in matig rendement met spontane afsplitsing van de beschermende groep op stikstof.



Om het toepassingsgebied van deze reactie uit te breiden, werd de reactie van α-chloorketimine (R_S)-**xxa** met isopropenylmagnesium bromide onderzocht. Deze keer werd de vorming van 3-aryl-3-pyrroline echter niet waargenomen en 2-isopropenylaziridine **xxiv** kon geïsoleerd worden als een stabiele verbinding in 69% rendement. De moeilijke reactie van α-chloorketimine (S_S)-**xxa** met 1-propenylmagnesium bromide geeft verder aan dat de graad van omlegging van 2-alkenylaziridinen beïnvloed wordt door subtiele sterische effecten uitgeoefend door de substituenten op de dubbele binding. Naast een aanzienlijke hoeveelheid gedehalogeneerd en niet gereageerd startmateriaal

(S_S)-**xxia** en (S_S)-**xxa**, waren zowel aziridine **xxvii** en 3-pyrroline **xxviii** aanwezig in het ruwe reactiemengsel. Na opzuivering echter, kon enkel 3-pyrroline **xxviii** geïsoleerd worden in laag rendement (13%, dr 86:14).



Samengevat kan gesteld worden dat de gesynthetiseerde 2-(carboxyethyl)aziridinen een waardevolle toevoeging zijn tot het arsenaal van gefunctionaliseerde aziridinen als synthetische bouwstenen, gezien het hoog synthetisch potentieel van deze 2-(carboxyethyl)aziridinen verder werd aangetoond *via* hun omzetting tot verschillende heterocyclische en carbocyclische verbindingen zoals γ-lactonen, γ-lactamen and cyclopropanen.

De gevormde 2-aminomethyl-gesubstitueerde 1-aminocyclopropaan-1-carbonzuurderivaten bleken excellente precursoren te zijn voor de synthese van een nieuw conformationeel beperkt analoog van (*S*)-2,4-diaminobutanoylpiperidine (Dab-Pip) en konden gebruikt worden als alternatieve α-aminozuren in korte peptiden om hun conformationele voorkeuren te onderzoeken.

Tenslotte konden chirale *N*-(*tert*-butanesulfinyl)-3-pyrrolinen en een 2-(isopropenyl)aziridine verkregen worden, startende van aromatische *N*-sulfinyl α-chloorketiminen.

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Publications in International Journals with Peer-Review ("a1")

1. **De Brabandere, S**.; Mangelinckx, S.; Kadam, S. T.; Nural, Y.; Augustyns, K.; Van der Veken, P.; Tornroos, K. W.; De Kimpe, N. "Synthesis of γ,δ-Aziridino-α-Amino Acid Derivatives and their Stereoselective Ring Transformation to 2-(Aminomethyl)-1-aminocyclopropanecarboxylic Acid Derivatives", *Eur. J. Org. Chem.* **2014**, 1220-1226.

2. Colpaert, F.; Mangelinckx, S.; **De Brabandere, S.**; De Kimpe, N. "Asymmetric Synthesis of α-Chloro-β-Amino-*N*-Sulfinylimidates as Chiral Building Blocks", *J. Org. Chem.* **2011**, *76*, 2204-2213.

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Conferences and Seminars

1. **De Brabandere, S.**; Kadam, S. T.; Nural, Y.; Augustyns, K.; Van der Veken, P.; Törnroos, K. W.; Formaggio, F.; De Kimpe, N.; Mangelinckx, S., Stereoselective synthesis of 2-(aminomethyl)-1-aminocyclopropanecarboxylic acid derivatives and their application in peptide design (*poster*), 17th Sigma Aldrich Organic Synthesis Meeting, Blankenberge, Belgium, 05-06 December 2013.

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5. Mangelinckx S.; **De Brabandere S.**; Kadam S. T.; Augustyns K.; Van der Veken P.; Törnroos K. W.; De Kimpe N., Synthesis of conformationally constrained heterocyclic and carbocyclic derivatives of 2,4-diaminobutyric acid (*oral communication*), COST Action CM0803, FOLDAMERS: Synthesis and structure of functional materials, Regensburg, Germany, 30/08-02 September 2012.

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